

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY

FIFTH EDITION

Edited and Revised by

C. LOVATT EVANS

D.Sc., F.R.C.P., F.R.S.

Jodrell Professor of Physiology, University College, London

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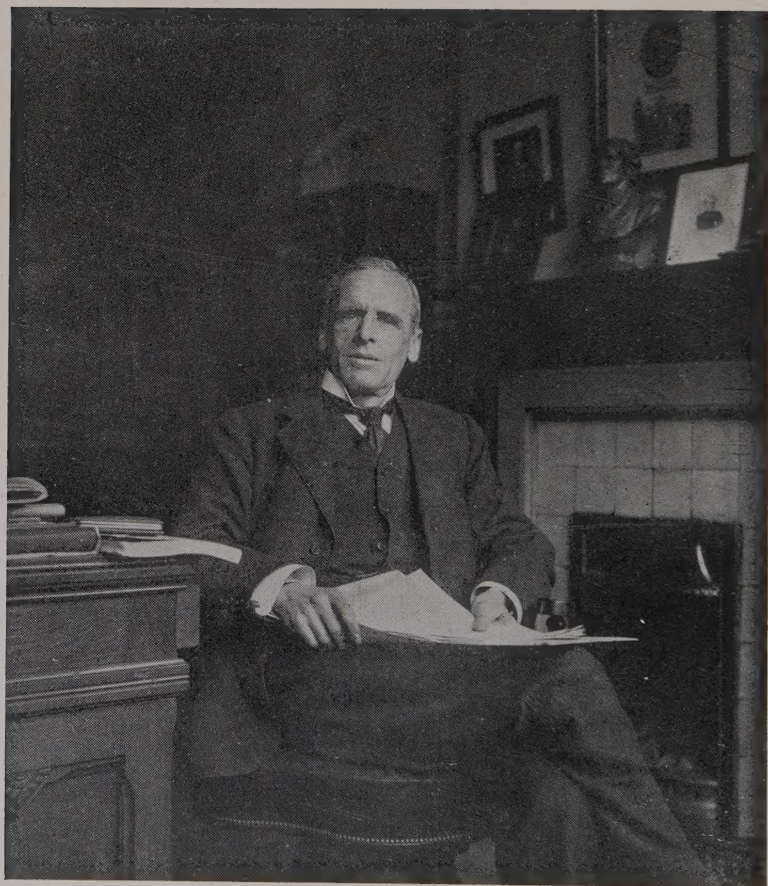
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Steve G

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May 1959

**PRINCIPLES OF
HUMAN PHYSIOLOGY**



ERNEST H. STARLING, C.M.G., F.R.S.

Born 1866. Died 1927.

(Photograph by Professor H. S. Raper.)

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THE CHAPTERS ON THE CENTRAL NERVOUS SYSTEM AND
SENSE ORGANS REVISED BY

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Professor of Physiology at St. Bartholomew's Medical College

WITH 543 ILLUSTRATIONS, 9 IN COLOUR



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PREFACE TO THE FIFTH EDITION

THE revision of this book has been no light task, and I may perhaps give briefly my reasons for having undertaken so heavy a responsibility. The chief and most compelling ones are purely sentimental.

I witnessed the preparation, by Starling, of the last edition, and read for him the proofs and made the index of the first. Just after the war he wrote inviting me to take over the major part of the revision for the preparation of the then forthcoming edition, saying with characteristic generosity, "If you can manage this, I should like you to consider yourself quite free in dealing with the text, in altering the arrangement, or in making additions and omissions—in short, that you impress some part of your personality on the new edition." The kind offer, which I was then compelled to decline, I now feel that I must accept, since it was clearly his wish.

If the rapidly growing complexity of physiology proved a source of embarrassment to my predecessor, with his broad knowledge and extensive experience, how much more must it be so for me? Among other things, I have attempted to adjust the general balance of the book, so far as this was indicated as desirable in the reviews (including my own) of the fourth edition, or was necessitated by recent work.

The work of revision would, I feel, have been insuperably difficult had it not been possible for me to draw directly upon the knowledge of others, and this I have done, without shame or compunction, whenever I wished to cover my own deficiencies or to confirm my own impressions. First among those who have come to my aid I must place Professor H. Hartridge, who has not only once more revised the chapters dealing with the special senses, but has also almost entirely rewritten the chapters on the Central Nervous System. The greater part of the book I have revised myself, and in those parts I know that there are few pages that have undergone no alterations, additions, or deletions. Although much new matter and about eighty new figures have been introduced, the bulk of the book is somewhat reduced; this is chiefly due to removal of old figures and to abbreviations of style.

For valuable advice and help dealing with the subjects which belong to them, I have especially to thank Professor J. C. Drummond, Dr. A. S. Parkes, Dr. R. J. Brocklehurst, and Dr. A. R. Fee; for help with the proofs, Dr. D. T. Harris, Mrs. G. P. Eggleton and Dr. Tookey Kerridge, but most especially Dr. R. J. Brocklehurst, who has read with characteristic thoroughness through the paged proofs.

Space will not allow of mention of the authors who have given permission for the use of figures, but these are acknowledged in the legends, and are here collectively thanked. I would, however, specially thank Dr. R. J. Ludford for having drawn Figures 3, 7, 528, and Dr. W. A. M.

Smart for Fig. 285 ; also Messrs. Longmans Green for the use of many blocks in Book III.

I wish to thank Messrs. J. & A. Churchill for the complete freedom they have allowed me, their artists for the excellence of their work, and Mr. J. Rivers for continued help and advice and for the preparation of the index.

C. LOVATT EVANS.

UNIVERSITY COLLEGE, LONDON.

PREFACE TO THE FOURTH EDITION

ALTHOUGH only five years have elapsed since the appearance of the last edition of this work, the progress in all branches of Physiology has been so rapid that it has necessitated extensive alterations in almost every chapter. Some parts have had to be entirely rewritten, on account of the revolution in our views that has been wrought by recent discoveries. The satisfaction that any physiologist must feel on contemplating this rapid advance is seriously tempered when it falls to his lot to present a general view of the whole of Physiology, embodying at their true value the results of investigations which range over every department of the Science.

I should indeed have found the task impossible but for the generous aid and continual inspiration which I have received from my fellow workers in this Institute. In the several sections dealing with the subjects which they have made their own, I am especially indebted for help to Dr. Anrep, Mr. R. K. Cannan, Dr. D. T. Harris, Professor A. V. Hill, Dr. Katz and Mr. A. S. Parkes. But I feel that my debt extends to all the workers in this laboratory, and that to them is due any success I may have achieved in this attempt to give a picture of Physiology as it stands to-day.

Although much new matter has been added, I have endeavoured in this edition to make the volume less bulky. The development of biochemical training has rendered it unnecessary to include even a summary of elementary organic chemistry in a text-book of Physiology. I have therefore been able to omit much that belonged strictly to the ancillary Sciences of Chemistry and Anatomy; and where it has seemed desirable to retain such matter it has been relegated to small print. Changes have also been made in the type and in the arrangement of chapters, which have resulted in a considerable saving of space and a shortening of the whole work.

In this, as in former editions, my wife has rendered me invaluable assistance both in the correction of proofs and in the ungrateful task of making the index.

ERNEST H. STARLING.

UNIVERSITY COLLEGE, LONDON.

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PHYSIOLOGY

CHAPTER I

INTRODUCTION

PHYSIOLOGY in its widest sense signifies the study of the phenomena presented by living organisms, the classification of these phenomena, and the recognition of their sequence and relative significance. The aims of physiology in its restricted sense are the description, analysis, and classification of the phenomena presented by the isolated organism, the allocation of every function to its appropriate organ, and the study of the conditions and mechanisms which determine each function.

The fundamental phenomena of life are essentially identical in all living organisms, and none can be regarded as outside the sphere of our investigations. The interest of mankind in this subject was, however, naturally awakened in connection with his own body, and the science, growing up as ancillary and preliminary to medical studies, has always taken man as its chief type of study. In the present work the elucidation of the functions of man will also be our first concern, and this for two reasons. In the first place, in physiology as in all other sciences, the motive of man's activity is his social instinct to increase the power of his race in the struggle for existence, by the acquisition of control, either over the external forces of nature, which may be turned to his own benefit, or over the factors, intrinsic and extrinsic, which tend to his enfeeblement or extirpation by disease and death. Consciously or unconsciously, all our researches in physiology, whether on the higher animals or on the lowest protozoa, have the welfare of man as their ultimate object. In the second place, the choice of the higher animals as our chief objects of study receives justification from the fact that, whereas morphology, or the science of structure, must proceed from the lowest to the highest organisation, the science of function presents its problems in their simplest form in the most highly differentiated organisms. In the unicellular animal all the essential functions which we associate with living beings are carried out, often simultaneously, in one little speck of protoplasm. An analysis of these functions, the determination of their conditions and mechanism, is obviously impossible under such circumstances. It is only when, as in the higher animals, one part of the living body is differentiated into an organ which has one function and one function only as the outlet for its activities, that it becomes possible to peer into the details of the function with some chance of discovering its ultimate mechanism.

Our especial preoccupation with the physiology of man will not prevent our employment of examples from any part of the animal or vegetable kingdom, when light can be thrown by their study on fundamental physiological phenomena common to the whole of the living world. In many cases such a study will enable us to separate the essential features in a

process from those which have been added as auxiliary, with increasing complexity of the structures concerned.

What are the fundamental phenomena which distinguish living beings? It is not possible briefly to define life without the idea being implicit in the definition. When dealing with the higher animals, we are inclined to lay greater stress on the phenomena involving a discharge of energy. Thus we should say that a man was alive if his body were warm and if he were presenting spontaneous movements, such as those of respiration or of the heart. The life of a man in the ordinary sense of the term is made up of those movements which place him in relationship with his environment. For the production of these movements, as for the maintenance of a constant body-temperature, a continual expenditure of energy is necessary. Experience teaches us that these movements come to an end in the absence of food or of oxygen, and that an increased call on the energies of the body must always be met by an increased demand for air and food. Two further processes must therefore be included among those making up our conception of life, viz. the function of assimilation (the taking in and digestion of food), and the function of respiration, by which oxygen is absorbed and carbon dioxide is excreted into the surrounding atmosphere.

The substances which make up our foodstuffs are all capable of oxidation. Composed chiefly of carbon and hydrogen, with some oxygen, nitrogen and sulphur, they yield, on complete combustion, carbon dioxide, water and small amounts of ammonia or allied bodies, and sulphates. In this process of oxidation there is liberation of heat. In the body a similar oxidation occurs, the products of oxidation being discharged into the surrounding medium. An amount of energy is thus set free which is available for the activities of the living organism. Before we can make any accurate investigations of the conditions which determine these activities, we must know whether the two great laws of chemistry and physics, viz. the conservation of mass and the conservation of energy, hold good for the processes within the living body. The many experiments which have been made on this point have decided the question in the affirmative. Thousands of experiments have been made, both on man and on animals, in which the total income of the body, viz. food and oxygen, has been weighed, and compared with the total output, viz. carbon dioxide, water, and bodies allied to ammonia (urea, &c.). In every case complete equality has been obtained, and we can be certain that any matter found in the body must have been derived from without. There is no creation or destruction of matter in the body.

The determination of the equation in the case of the total energy of the body is rather more difficult. We have, in the first place, to measure the total income and output of the body, and to determine the total heat which would be evolved by the oxidation of the foodstuffs ingested to the carbon dioxide, water, &c., that are given out. We must then compare the figure so obtained with the actual output of energy by the body. The latter can be measured in terms of heat by placing the animal inside a calorimeter. Many practical difficulties arise in the performance of the experiment, in consequence of the necessity of providing the animal with a constant supply of air to breathe, and of allowing for the continual loss of water by evaporation which is going on at the surface of the animal. The first accurate experiments of this nature were made by Rubner. This observer determined by means of the calorimeter the total heat loss of dogs. In the same animals the material income and output of the body were measured, and a calculation was made as to the amount of energy which would be set free in the body

by the processes of oxidation involved in the change of material observed. The following Table represents a summary of Rubner's results :

Dog.	Condition of dog.	Calculated heat production.	Heat loss determined calorimetrically.	Duration of experiment.
		Cal.	Cal.	Days.
1.	Fasting	259.3	261.0	5
2.	"	545.6	528.3	2
3.	Fed with meat	329.9	333.9	1
4.	Fed with fat	302.0	299.1	5
5.	Fed with meat and fat	332.1	330.0	12
6.	" "	311.6	331.0	8
7.	Fed with meat	375.0	379.5	6
8.	" "	683.0	681.3	7

It will be seen that the average difference between the calculated and observed results amounts only to 1.01 per cent.—an amazing agreement considering the extreme difficulties of the experimental methods involved. The important deduction to be drawn from these observations is that the foodstuffs which are oxidised in the body develop in this process exactly the same amount of energy as when they are burnt up outside the body.

The law of the conservation of energy is often spoken of as the first law of thermodynamics. It asserts that, while energy may be of various kinds, kinetic, thermal, chemical, electrical, &c., which can be converted into one another, there is never any gain or loss in the conversion. Energy has been defined as the capacity of doing work. But while many forms of energy are interconvertible and can be transformed into work almost without loss, or can be converted into heat, the reverse change of heat into work is possible only under certain conditions. Of the total energy contained in a system, only that part which can be utilised in the production of work is of value. This is the 'free energy' of the system. The second law of thermodynamics states that free energy is always striving to a minimum. This law has also been enunciated as the law of 'the dissipation of energy.' It implies necessarily the impossibility of perpetual motion. Though exceptions to this law, as in Maxwell's 'demon,' are conceptually possible, all evidence is in favour of its strict applicability to the processes of the living cell—as well as to all those of which we have experience in the world around us.

From one aspect, therefore, the animal body may be looked upon as a machine for the transformation of the potential energy of the foodstuffs into kinetic energy, represented by the warmth and movements of the body as well as by other physical changes involved in vital processes. In the living organism we cannot however distinguish between the source of energy and the machinery, as we can in the case of our engines. When we endeavour to trace the foodstuffs after their entry into the body, we lose sight of them at the point where they are built up to form apparently an integral part of the living framework. During activity there is a discharge of the products of oxidation of the foodstuffs from this living matter, which therefore becomes reduced in mass. This reduction, or disintegration of the living matter, associated with activity, is always followed by a period of increased integration, during which the organism grows by the assimilation of more food. Our conception of life must therefore involve the idea of a constantly recurring cycle of processes, one of building up, repair, or integration, and the other, associated with activity, of destruction or disintegration. If the former process predominates, we obtain a steady increase in the mass of the organism, an increase which we speak of as growth, and in many cases, as in that of plants, it is this power of growth which we take as our criterion of the existence of life. In fact, the possession by the green parts of plants of the power of

utilising the energies of the sun's rays for the integration of foodstuffs, such as starch, with a high potential energy, is the necessary condition for the existence of all higher forms of life on this earth.

Closely associated with the property of growth is the power possessed by all living organisms of repair, *i.e.* the replacement by newly formed healthy living material of parts which have been damaged by external events.

The process of growth does not, in the individual, proceed indefinitely. At a certain stage in its life every organism divides, and part of its substance is thrown off to form one or more new individuals, each of them endowed with the same properties as the parent organism, and destined to grow until it is indistinguishable from the organism whence it was derived. In the lowest forms of life, the unicellular organisms, these processes of growth and division may go on until brought to an end by some change in the environment which will not allow the necessary conditions of life, *viz.* assimilation and disintegration, to proceed. In all the higher forms however, after the process of reproduction has been completed, the parent organism begins to undergo decay, however favourable the environment, and the processes of assimilation and repair no longer keep pace with those of destruction, until finally death of the organism takes place.

All these phenomena, *viz.* assimilation, respiration, activity associated with the discharge of energy, growth, reproduction, and death itself, are bound up in our conception of life. All have one feature in common, *viz.* they are subject to the statement that every living organism is endowed with the power of *adaptation*. Adaptation may indeed receive the definition which Herbert Spencer has applied to life—"the continuous adjustment of internal relations to external relations." A living organism may be regarded as a highly unstable system which tends to increase itself continuously under the average of the conditions to which it is subject, but undergoes disintegration as a result of any variation from this average. It is evident that the sole condition for the survival of the organism is that any such act of disintegration shall result in so modifying the relation of the system to the environment that it is once more restored to the average in which assimilation can be resumed. Every phase of activity in a living being must be not only a necessary sequence of some antecedent change in its environment, but must be so *adapted* to this change as to tend to its neutralisation, and so to the survival of the organism. This is what is meant by adaptation. Not only does it involve the teleological conception that every normal activity must be for the good of the organism, but it must also apply to *all* the relations of living beings. It must therefore be the guiding principle, not only in physiology with its special preoccupation with the internal relations of the parts of the organism, but also in the other branches of biology, which treat of the relations of the living animal to its environment and of the factors determining its survival in the struggle for existence. The origin or survival of new species and the succession of the different forms of life upon this earth depend on the varying perfection of the mechanisms of adaptation.

We may imagine that the first step in the evolution of life was taken when some compound was formed, probably with absorption of heat, endowed with the property of continuous polymerisation and growth at the expense of surrounding material. Such a substance could continue to exist only at the expense of the energy derived from the surrounding medium, and would undergo destruction with any stormy change in its environment. Out of the many compounds of this nature which might have come into being, only those would survive in which the process of exothermic disintegration tended towards a condition of greater stability, so that the process would come to an

end spontaneously, and the organism or compound be enabled to await the more favourable conditions necessary for resuming its growth. With the continued cooling of the earth, the new production of endothermic compounds would become rarer and rarer; and in all probability the beginning of life, as we know it, was the formation of some complex substance, analogous to the present chlorophyll corpuscles, with the power of absorbing the newly penetrating sun's rays and utilising them for the endothermic formation of further unstable compounds. Once given an unstable system, such as we have imagined, the great principle laid down by Darwin, viz. survival of the fittest, will suffice to account for the production from it by evolution of the ever-increasing variety of living beings which have appeared in the later history of this globe. The 'adaptation,' i.e. the reactions of the primitive living material to changes in its environment, must become ever more and more complex, since only by means of increasing variety of reaction is it possible to provide for the stability of the system within greater and greater range of external conditions. The difference between higher and lower forms is therefore one of complexity of reaction, or of range of adaptation.

In all the physiological processes which we shall study in the course of this work, adaptation will be found the constant and guiding quality. The naked protoplasm of the plasmodium of *Myxomycetes*, if placed on a piece of wet blotting-paper, will crawl towards an infusion of dead leaves, or away from a solution of quinine. It is the same property of adaptation, the deciding factor in the struggle for existence, which impels the greatest thinkers of our time to spend long years of toil in the invention for their community of the means for offence and defence, or for the protection of mankind against disease and death. The same law which determines the downward growth of the root in plants is responsible for the existence to-day of all the sciences of which mankind is proud.

This "adjustment of internal to external relations" is possible only within strictly defined limits, limits which increase in extent with rise in the type of organism, and in the complexity of its powers of reaction. Some of these limiting conditions we shall have to study in the next chapter. Among the chief of them are temperature, and the presence of food material and of oxygen. At the present time the limits of temperature may be placed between 0° and 50° C. Many organisms are killed by the alteration of only a few degrees in the temperature of their environment. Every shifting of a cold or warm current in the Atlantic, in consequence of storms on the surface, leads to the destruction of myriads of fish and other denizens of the sea. In the higher animals a greater stability in face of such changes has been accomplished by the development of a heat-regulating mechanism, so that, provided sufficient food is available, the temperature of the body is maintained at a constant level, which represents the optimum for the discharge of the normal functions of the constituent parts of the body. The presence of food material in the environment of the living organism is a necessary condition for its continued existence. In some cases, and this we must assume to be the primitive condition, the food material must be of a given character and form a constant constituent of the surrounding medium. In the higher forms, the development of a complex digestive system has enabled the organism to utilise many different kinds of food, while the storage of any excess of food as reserve material, temporarily provides for a constant supply of food to the constituent cells of the body, even when it is quite wanting in the environment. Since plants depend for their food in the first place on the carbohydrates produced within the chlorophyll corpuscles out of the atmospheric carbon dioxide by the energy

of the sun's rays, necessary conditions for their existence will be sunlight and the presence of this gas in the surrounding atmosphere.

One other necessary condition for the existence of life is the presence of water. Although this substance cannot furnish any energy to the complex reactions taking place in the cell, it is an essential constituent of all living matter, and plays a part in all the changes which determine the transformations of matter and energy in the organism.

This short summary of the chief characteristics of living beings would be incomplete without the mention of what is perhaps their distinctive feature, namely, *organisation*. Although little marked in the lowest members of the living kingdom, where we can detect only a speck of structureless material containing a few granules, of which one (or more) is distinguished by the name of nucleus, in the higher members this organisation becomes more and more marked. This greater complexity of organisation, which we often speak of as histological differentiation, runs parallel with increasing range of power of adaptation, and with growing efficiency of adaptive reactions attained by the setting apart of special structures (organs) for the performance of definite functions. The parallelism between the development of function and structure justifies us in the assumption generally, though often only tacitly, made by physiologists, that the structure is the determining factor for the function. We might regard the histological differentiation as representing merely a continuation of the increasing molecular complexity, which we assumed must accompany and determine every widening in the range of the adaptive power of the organism. Further, as living animals show progressively increasing differentiation of structure in all their parts, and with this an increased power of adaptation of each part, so by increasingly delicate co-operation between their various parts, they display a progressive advance in *integration* which further augments the powers of the individual to adapt itself to its surroundings.

To sum up. Our objects in the study of physiology include the description of the chief reactions of the body to changes in its environment, the analysis of these reactions into the simpler reactions of which they are made up, and the assignment to each differentiated structure of the organism its part in every reaction. We must determine the conditions under which each reaction takes place, so that we may learn to evoke any part of it at will by application of the appropriate stimulus, *i.e.* by effective change of environment.

A reaction involves expenditure of energy, and this can be derived only from chemical change in the reacting organ, and ultimately from the disintegration or oxidation of the foodstuffs. Our next task must therefore be the analysis of the energetic and material changes, with a view to determining the whole sequence of events, from the occurrence of the external exciting change to the finished reaction, which will alter in the direction of protection the relation of the organism to its environment. In short, it is the office of physiology to discover the routine sequence of events in the living organism under all manner of conditions. In attacking this problem our methods cannot differ fundamentally from those of the physicist and chemist. In every case our experiments will consist in the observation and measurement of movements of one kind or another which we shall interpret in terms of mass or energy. Physiology, if it could be completed, would therefore describe the *how* of every process in the body. It would state the sequence of events and would summarise these as so-called 'laws.' These laws would however no more explain the phenomena of life than does the 'law of gravitation' explain the fact that two masses tend to move towards one

another with uniform acceleration. Nor can we hope to explain physiological phenomena by reference to the laws of physics and chemistry, since these themselves are only expressions of sequences, and not explanations. With every growth in science however, its generalisations become wider and its laws summarise ever more extensive groups of phenomena. We have no reason for asserting that, in the course of research, we may not finally succeed in describing vital phenomena in the "conceptual shorthand" * used by the physicist, involving his ideal world of ether, atom and electron. At present we are far from such a consummation. The principle of adaptation is the only formula which will include all the phenomena of living beings. This principle must provisionally be accepted as fundamental by the biologist, as the physicist accepts the first law of thermodynamics.

The difficulty, which must be felt with greater force the more deeply the physiologist endeavours to peer into the processes within the living cells, has led some, even at the present day, to the assumption of a special quality in living organisms which is designated as 'vital force' or 'vital activity.' Such views are classified together under the term 'vitalism.' From his beginning man has been accustomed to draw a sharp line of distinction between those phenomena which by their constant occurrence seemed to him explicable, and those phenomena of which he could not see the determining antecedent, and which were to him therefore anomic and capricious. To the latter he set up graven images and, not perceiving his own springs of action, endowed them with a self-determining personality such as he imagined himself to possess. Such a graven image is vitalism. As a working hypothesis it must be sterile. In many cases however, the terms 'vitalism' and its antithesis 'mechanism' are used unjustifiably. Although the phenomena of living matter are not arbitrary, the conditions are infinitely complicated when compared with those concerned with the study of non-living matter, and hence more difficult to control. The physiologist, basing his belief in the principle of adaptation, must reject vitalistic "explanations" and seek to discover by experiment the conditions which determine the appearance of phenomena in living things. But he must equally reject an arrogant and superficial doctrine of "mechanism" which would suppose that life can be the outcome of any chance encounter of physical and chemical phenomena, and here again the principle of adaptation must be his guide, in refusing to accept the suggestion that physiology is nothing more than applied chemistry and physics. Holding this principle always before him, he must abide by the answer he receives from his experiments as to the ways and means of adaptation, and can hope for little more.

Throughout this chapter we have assumed no necessary dividing line between the different classes of phenomena in the conceptual universe, although in the present state of our knowledge we are far from being able to include the whole of them under the same general laws. It might be objected that in taking up this attitude we have left out of account one supreme fact, viz. the existence of *consciousness* in ourselves. As a comparative and objective study however, physiology is concerned, not with the study of consciousness, but with the conceptions in consciousness of the *phenomena* presented by living beings. Consciousness in fact we know only in ourselves. From the actions of other living beings similarly organised, we infer in them the existence of a similar consciousness. Again, from the fact that the reactions of the higher mammals are evidently determined, not by immediate impressions but largely by stored-up impressions of past stimuli,

* Karl Pearson, "Grammar of Science," p. 328 *et seq.* (2nd ed.).

we credit them also with a certain but lower degree of consciousness. As we descend the scale of animal life, evidence of the existence of consciousness, as we know it, rapidly diminishes and finally disappears, though it is impossible to draw a sharp line between those animals which possess consciousness and those in which it is absent. That it is a necessary accompaniment of life is certainly not the case. Consciousness is in fact connected with the possession of a highly developed central nervous system, and its degree is in proportion to the complexity and activity of this system. Since the brain with all the other organs of the body is derived from a simple cell, the fertilised ovum, similar in its absence of differentiation to the lowest organisms, it might be argued that all types of life are endowed with something which is not consciousness, but which has the potentiality of developing into consciousness. We have however no means of judging of the presence or absence of this hypothetical quality, and still less of determining whether it is a property of living substance only or is shared also by the atoms of so-called dead material.

THE METHOD OF PHYSIOLOGY.—In the prosecution of his enquiries the physiologist often must make appeal to other sciences, but especially to chemistry and physics. In the first place the chemistry and physics of the various separate organs of the animal body must be investigated. This involves first an accurate knowledge of the gross and minute structures, and hence requires the aid of anatomy and histology. Here very frequently, too, comparative anatomy and histology furnish valuable clues to function.

Then the chemical, physical and physico-chemical build must be taken into consideration with a view to the determination of the changes which these exhibit under altered conditions of environment, chemical or physical in nature.

In this way analytical physiology is built up, by experiments, carried out on living animals, or on separated parts of them surviving for a time under suitable conditions; knowledge of the properties and functions of the various structural parts is obtained. Then, in synthetic physiology we attempt to find how, by integrative processes, the functions of the body as a whole are synthesised from the co-operative activity of the various parts, and how the organism as a whole reacts, by appropriate adjustment of its individual organs, to changes in its external environment.

BOOK I

GENERAL PHYSIOLOGY

CHAPTER II

THE STRUCTURAL BASIS OF THE BODY

THE CELL

ALL the higher animals and plants, when submitted to microscopic examination, are seen to consist of structural units which are spoken of as cells. Each organ is a mass of these cells and, since the formulation of what is

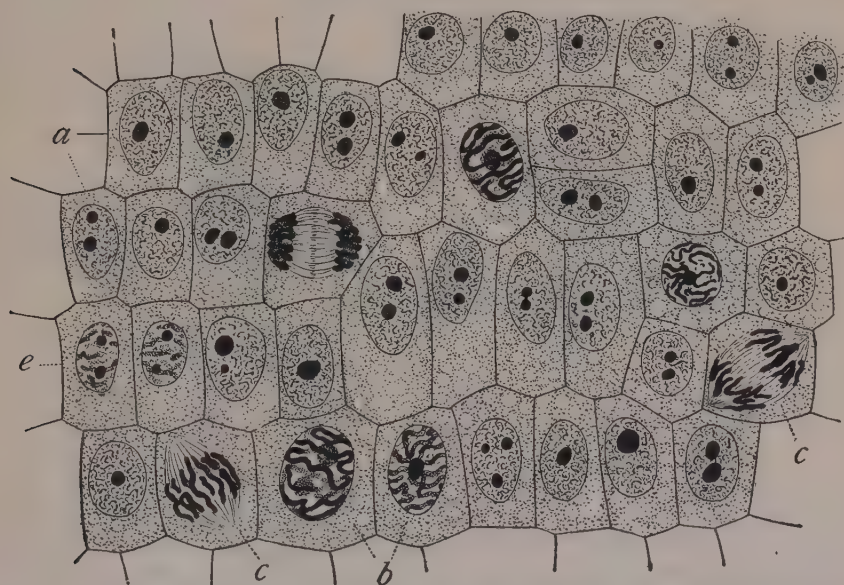


FIG. 1. General view of Cells in the growing Root-tip of the Onion, from a longitudinal section enlarged 800 diameters. (WILSON.)

a, non-dividing cells, with chromatin network and deeply stained nucleoli;
b, nuclei preparing for division (spireme stage); *c*, dividing cells showing mitotic figures; *e*, pair of daughter cells shortly after division.

called the *cell theory* of life by Schwann and Schleiden about 1840, it has been customary to regard the function of any organ, or indeed of the whole body, as the sum of the functions of its constituent cells. The cell is therefore the physiological as well as the structural unit, and it is necessary to commence our study of the functions of the animal body with some consideration of the functions and reactions which are common to all these units.

Amongst the lower forms, both animal and vegetable, an immense number of organisms consist only of a single cell. In this cell are represented all the phenomena of life, all the adapted reactions which we associate with the life of the higher organisms. That the unicellular condition represents the more primitive stage, from which the higher organisms have been evolved in the course of ages, is indicated by the fact that every one of these higher organisms

in its development commences with an unicellular stage, namely, the fertilised ovum. We assume that the series of changes attending the development of the higher organism from the egg is a repetition in summary of the changes which have determined the evolution of the species from the primitive unicellular type.*

The general characteristics of the cell present important similarities, whether we are considering a cell which forms the whole of an organism or a cell which is but an infinitesimal part of a highly developed animal.

The name 'cell' was first applied by botanists to the structural units found by them in plant tissues, and involved the idea of certain qualities which do not enter into our present conception of the term. A section through the stem of a growing plant shows it to be made up of an aggregation of cells in the etymological sense of the word, *i.e.* small sacs bounded by a wall of cellulose and containing cell sap. Immediately inside the cellulose wall is a thin layer, the primordial utricle, which encloses at one

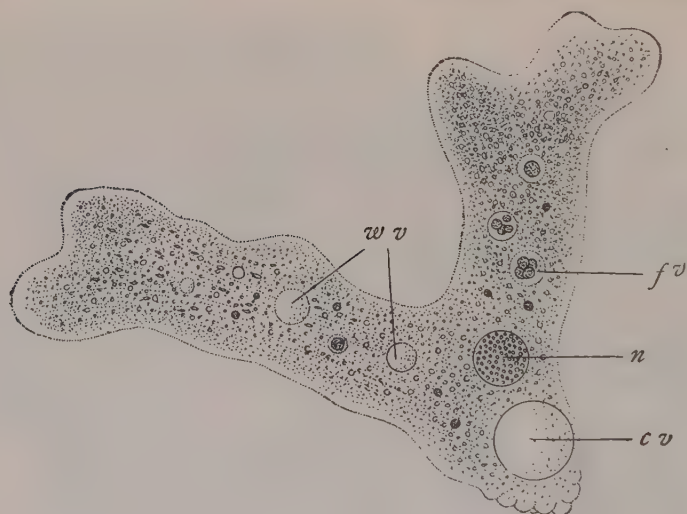


FIG. 2. *Amoeba proteus*, an Animal consisting of a single naked Cell, $\times 280$.
(From SEDGWICK and WILSON'S "Biology.")

n, the nucleus; *wv*, water vacuoles; *cv*, contractile vacuole; *fv*, food vacuole.

point a spherical or oval structure known as the nucleus. If the section be taken from the growing tip of a plant (Fig. 1), the cell sap is found to be wanting, and the cells consist only of the substance known as protoplasm, which later on will form the primordial utricle. This, with a nucleus, is enclosed in a delicate cellulose wall. The wall is not an essential constituent, since it is absent from many vegetable cells at some period of their life and from animal cells generally.

A better conception of the essentials of a cell can be obtained by the study of an unicellular animal such as an amoeba (Fig. 2). This is an organism frequenting stagnant pools, of varying size (from 0.1 to 0.3 mm. in diameter), apparently of a semi-fluid consistence. When first examined it is generally spherical, but in a short time begins to change its form, putting out processes known as pseudopodia. By shifting the distribution of its material among these processes, it is able to move about and also to ingest particles of food or pigment with which it may come in contact. Near its centre a differentiated

* This assumption is often spoken of as the 'law of recapitulation.'

portion can be distinguished which is known as the nucleus. The rest of the amœba, the protoplasm or cytoplasm, often presents further differentiation into an outer clear layer and an inner finely granular substance. The latter may contain coarser granules, some of food material, others apparently formed *in situ* by the surrounding protoplasm, and often small vacuoles ('contractile vacuoles') which are continually altering their size and serve to keep up a circulation of fluid in the interstices of the cytoplasm. In all cells, whether animal or vegetable, with which we are acquainted, this twofold structure is also found. So we may define a cell as a small mass of protoplasm containing a nucleus.

Every cell, so far as we have been able to ascertain, is derived from some pre-existing cell, by a process of division, and every nucleus similarly from a parent nucleus. These important laws, so significant in the study of heredity, were expressed by Virchow (1855) and Flemming (1882) in the dicta "*omnis cellula e cellula*" and "*omnis nucleus e nucleo*" respectively. As a necessary consequence it follows that the cytoplasm of the cell is also derived from the previously existing cytoplasm of the cell from which it arose.

Doubt has often been expressed whether a nucleus is to be regarded as essential to our conception of a cell. In many of the lowest forms of animals and plants, such

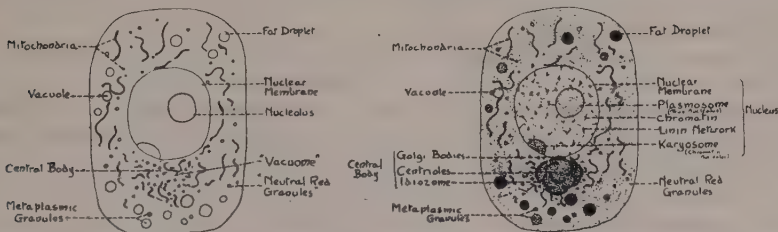


FIG. 3. Diagram to show contents of typical cell. On left, structures which can be seen under appropriate conditions in the living cell. On right, the structures demonstrable by various fixing and staining methods. (LUDFORD.)

as the Flagellata among the former and the Cyanophyceæ and Bacteria among the latter, no distinct nucleus can be demonstrated. In many of these forms the dimensions of the whole organism are too minute to allow of any definite statement being made as to the presence or absence of nuclear material. In the larger of them, however, the cytoplasm of the cell contains numerous scattered granules which stain with dyes in the same way as do the nuclei of the cells of higher animals, and these granules possess the resistance to the action of certain digestive fluids which is typical of nuclei. They may therefore be taken as representing the nucleus in the higher forms. Even in the latter at certain stages, namely, during the division of the cell, the nucleus breaks up into discrete parts, and there is no reason for believing that such a scattered condition of the nuclear material may not last throughout the whole life of the cell.

We have defined a cell as a small mass of protoplasm containing a nucleus. Since we shall have to use the term 'protoplasm' on many occasions in the course of this work, we must have a definite conception of what we mean by it. The term is often used by histologists as implying a substance of certain definite chemical and staining characters. When employed by physiologists it generally implies any material which we can, on a study of its behaviour to changes in its environment, regard as endowed with life. Huxley has defined it as "the physical basis of life." Though it may be convenient to have a word such as protoplasm signifying simply 'living material,' it is important to remember that there is no such thing as a single substance—protoplasm. The reactions of every cell as well as its organisation are the resultant of the molecular structure of the matter of which it is built up.

The gross methods of the chemist show him that the composition of the 'protoplasm' of the muscle cell is entirely different from that of a leucocyte or white blood corpuscle. The finer methods of the physiologist show him that every sort of cell in the body has its own manner of life, its own peculiarities of reaction to uniform changes in its surroundings. No individual will react in exactly the same manner as another individual, even of the same species, and the reactions of the whole organism are but the sum of the reactions of its constituent cells. There is not *one* protoplasm therefore, but an infinity of protoplasms, and the use of the term can be justified only if we keep this fact in mind and use the word merely as a convenient abbreviation for any material endowed with life. Even in a single cell there is more than one kind of protoplasm. In its chemical characters, in its mode of life, and in its reactions, the nucleus differs widely from the cytoplasm. Both are necessary for the life of the cell and both must be considered, according to our present ideas, as 'living.' In the cytoplasm itself we find structures or substances which we must regard as on their way to protoplasm or as products of the breakdown of protoplasm; but in many cases it is impossible to say whether a given material is to be regarded as lifeless or as reactive living matter. Even in a single cell we may have differentiation among its different parts, one part serving for the process of digestion while others are employed for the purpose of locomotion. Here again there must be chemical differences, and therefore different protoplasms. In this book the term protoplasm will be used in its broadest sense, namely, as the physical basis of living organisms.

VITAL PHENOMENA OF CELLS. A. *Assimilation.* The activity of every living being can be regarded as compounded of two phases, *assimilation* and *dissimilation*. By assimilation we mean the building up of the living substance at the expense of material obtained from the external world. In this process substances are formed of high potential energy, and this energy is obtained either from that imparted to the system at the moment of assimilation, as *e.g.* in the assimilation of carbon from carbon dioxide under the influence of the sun's rays, or from that contained in the food-stuffs themselves. In animal cells it is the latter method which is adopted and a foodstuff therefore connotes some substance which can be taken in by the cell and can serve it as a source of chemical energy. The energy required for the movements and other vital activities of the cell is derived from a disintegration or dissimilation of the protoplasm, generally associated with the process of oxidation. In assimilation, besides the building up of living protoplasm, there may also be a synthesis of more complex from less complex compounds, without their necessary entry into the structure of the living molecule. In the absence of any definite criteria by which we may judge as to the living or non-living condition of parts of the cell, it is a little dangerous to draw any hard-and-fast distinction between these two sets of processes. Assimilation requires the ingestion of food into the organism, and then its digestion, *i.e.* its solution in the juices of the cells. These two processes are succeeded, through stages which we cannot trace, by an actual growth in the living material. In naked cells ingestion may occur either at any part of the surface, as in the amoeba, or at a specialised portion, so-called 'mouth,' as in many of the infusoria. Digestion is apparently effected in most cases by the production and secretion around the ingested food particles of solutions containing *enzymes*, *i.e.* agents which have the power of hydrolysing the different foodstuffs and thus rendering them soluble.

In the vast majority of living organisms the energy for their activities

is derived from the oxidation, ultimately of the foodstuffs, but immediately of molecules attached to the living protoplasm. A necessary condition therefore for the life of these cells is the presence of oxygen in the surrounding medium, from which it is taken up in the molecular form. As a result of this oxidation, products are formed which are of no further value to the cell and are therefore excreted, *i.e.* turned out of the cell. The chief of these are the products of oxidation of carbon and hydrogen, namely, carbon dioxide and water. There are also many substances resulting from the oxidation of the nitrogenous portions of the protoplasm which have to be excreted in the solid or dissolved form.

Although the assimilation of oxygen is so general a quality of living protoplasm, the presence of this gas, at any rate in the free form, does not seem to be necessary for all kinds of life. Thus many bacteria are known which are anaerobic, *i.e.* exist only in the absence of oxygen. Examples of such are bacillus tetanus and the bacillus of malignant oedema. These organisms derive the energy for the building up of their protoplasm, for their movements, &c., not from a process of oxidation, but from processes of disintegration of the substances which they utilise as food. It is by such means that in all probability the intestinal worms, fairly highly organised animals, are able to exist in the intestine in a medium containing no oxygen, but rich in carbon dioxide. Here they are plentifully supplied with foodstuffs and can afford to adopt a wasteful method of nutrition, in which only a small fraction of the energy is obtained which would be produced by a total oxidation of the food.

B. The Phenomena of Dissimilation. The activities of a living cell or organism can be regarded in every case as dependent originally on environmental change, and are adapted to this change, *i.e.* are of such a nature that they tend to preserve the organism intact, to favour its growth, or prevent its destruction. The property of reacting in such a manner to changes in the environment is fundamental to all protoplasm and is spoken of as *excitability*, and the change which will influence an organism and cause a corresponding adaptive change in it is known as a *stimulus*. Stimuli may be of various kinds. Thus mechanical, thermal, chemical, electrical changes, light and so on may act as stimuli. The reactions which they evoke involve in every case chemical changes in the protoplasm, *i.e.* changes in the metabolism of the cell. Sometimes this change may be assimilatory in character, leading to an increased growth of the protoplasm, or at any rate to a cessation of dissimilation. In such a case the stimulus is spoken of as inhibitory, because it diminishes or prevents the output of energy by the organism. The frequent result of a stimulus is an increased output of energy, which may appear in the form of movement, in the form of heat, or as chemical change.

A common feature of all dissimilatory changes evoked by the application of a stimulus is that the energy of the reaction is many times greater than the energy represented by the stimulus, the excess of course being supplied at the expense of the potential energy of the food material which has been stored in or built up into the living protoplasm. This disproportion between stimulus and reaction can be well illustrated on an excitable tissue such as muscle. Thus in one experiment the gastrocnemius muscle of a frog was loaded with a weight of 48 grammes. The nerve running to the muscle was placed on a hard surface and a weight of half a gramme was allowed to fall upon it from a height of 10 mm. The muscle contracted in response to this mechanical stimulus applied to the nerve and raised the weight 3.8 mm. In this case the work performed by the muscle was $48 \times 3.8 = 182.4$ gramme-mm., while the potential energy of the stimulus represented only $0.5 \times 10.0 = 5.0$ gramme-mm. Thus the work performed by the muscle was thirty-six times larger than the energy of the stimulus applied to the nerve,

In the case of unicellular organisms, definite classes of motor reaction to stimulus have been described. Among the primitive reactions of cells perhaps the most important in the life of higher animals are those grouped under the term *chemiotaxis*. In the fertilisation of the ovum in the prothallus of ferns by the antherozoids it was shown by Pfeffer that the movement of the antherozoids towards the ova is effected in response to a chemical stimulus, probably malic acid. In the same way aerobic bacteria are attracted by the presence of oxygen. If such bacteria are present in a solution with an alga, on exposure of the fluid to light there is an evolution of oxygen by the green alga, and a consequent congregation of the bacteria round the seat of production of the oxygen. The movements of the white corpuscles of the blood of the higher animals are also largely determined by their chemical sensibility, and various substances can be divided into (a) those which exercise positive and (b) those which exercise negative chemiotactic influence on the leucocytes. Thus the introduction under the skin of an animal of a capillary tube containing a solution of substances of the first class, such as peptone, tissue extracts, or the chemical products of certain bacteria, leads to an accumulation within the tube of leucocytes which pass to it from all the surrounding tissues. Other substances, such as quinine, exert a negative chemiotaxis. Tubes filled with these, after introduction into the subcutaneous tissue of a mammal, will be found many hours later to contain no leucocytes at all.

METHODS EMPLOYED IN THE STUDY OF MINUTE STRUCTURE. The study of structure for its own sake properly belongs to the

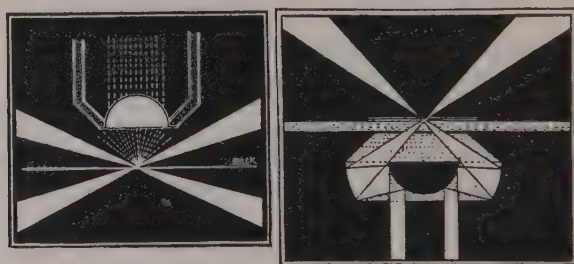


FIG. 4. To illustrate the principle of dark-ground illumination, and the method by which this is obtained with the use of a special substage condenser. (Courtesy of Messrs. R. and J. BECK.)

subject of anatomy and histology, but the relations between structure and function are so intimate that the science of physiology would be incomplete if it did not take considerations of structure into account. Moreover, there has grown up recently an important branch of physiological investigation, namely, the enquiry into the physiology of individual cells, in which methods of histological research are in constant use.

The microscope is, of course, the chief implement used by the histologist, and with the assistance of the customary histological technique for preparation of material, the structure of all the organs and tissues of the body has been thoroughly explored. This histological technique, however, has its limitations. We are often in doubt as to how far the structures we see in fixed and stained preparations have any real existence in the living cells. Moreover, the power of the microscope to reveal minute details appears to have been developed to the uttermost limit, namely, to enable us to see structures whose dimensions are of the same order as the wave-length of light. Some further resolution can be got by using light of shorter wave-lengths; more detail will be seen with green illumination of wave-length of, say, 5,500 A.U. than with yellow light of wave-length 6,000 A.U., and by photomicrography with invisible ultra-violet light of wave-length 3,000 A.U. still more details could be unfolded. A further result of using ultra-violet light has been to show that certain structures are more opaque to it than others, though both

types may be equally transparent to the visible rays ; hence not only finer structures, but actual new structures, may be revealed.

A further refinement is by the use of the principle of the ultra-microscope in what is called *dark-ground illumination*. With the aid of a paraboloid condenser the light is thrown nearly transversely across the preparation (Fig. 4), so that the field is dark except where particles lying in the path of the beam are able to reflect the light into the microscope. This method will reveal the position of particles in living protoplasm, and give us some

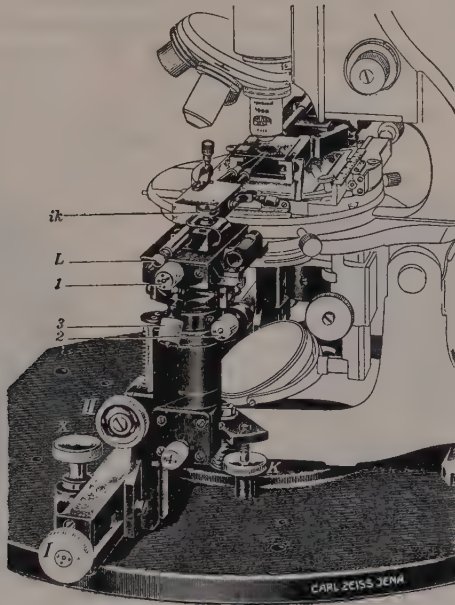


Fig. 5. Micro-manipulator in position. It consists of a rigid base on which is mounted the microscope, and on either side of this an operating stand. The manipulations are in the main effected by six screws, two of which transmit coarse motions to the operating stands as a whole, while the other four screws serve to actuate the micro-instruments. I. Coarse perilateral screw ; motion, from right to left, and *vice versa*. II. Coarse vertical screw ; motion, in an up and down direction. 1. Fine perilateral screw. 2. Fine sagittal screw ; motion, forward and backward, and *vice versa*. 3. Diagonal screw ; motion, radially up and down. 4. Fine vertical screw. In the figure a double needle is shown on one stand and a single one on the other. (Courtesy of Messrs. CARL ZEISS.)

idea of their size, even though they are so small as to be invisible by any direct microscopic examination.

Much valuable information has been obtained with regard to the structure and behaviour of living cells by means of *micro-manipulation*, or micrurgical technique, which has been extensively used by Chambers as a means of dissecting the live cell or of injecting various fluids into it. The living cells are suspended, as a hanging-drop preparation, from a cover-glass, and are manipulated and dissected by means of two fine glass needles, the movements of which in all directions are controlled by micrometer adjustments (Fig. 5). In dissection one needle is brought up so as to hold the cell or tissue while the other needle is employed to dissect it, the whole operation and its results being watched under the microscope : injection is performed by fixing the cell with a needle and then perforating it at

the desired place with a fine glass capillary through which the fluid is then forced from a micrometer syringe.

Another method which has found many applications of late is that of *tissue culture*, in which small portions of embryonic tissue are taken and kept at suitable temperatures in a nutrient fluid, such as a mixture of embryo extract, blood plasma and saline solution. The whole preparation must be aseptic, and is usually made as a hanging drop in a chamber and sealed off from the air with vaseline. The tissue continues to live, and under certain conditions the cells grow and multiply in an apparently normal manner until the cell mass reaches a certain size, when growth ceases and degeneration sets in unless a small piece of the tissue is taken and used to start another similar culture. In some cases the process of sub-culture can apparently be

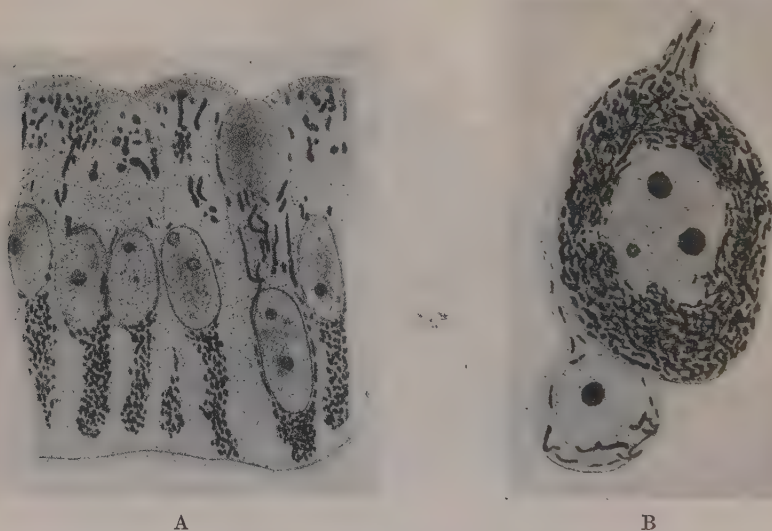


FIG. 6. Various Cells stained to show Mitochondria. (E. V. COWDRY.)

A. Lining Cells of the Small Intestine.

B. Two Nerve Cells, with different forms of Mitochondria.

repeated indefinitely. Much has been learned of the structure, growth, and differentiation of embryonic cells by this method.

The histological staining methods are very usefully supplemented by a variety of so-called *intra-vitam staining* methods in which the dye is presented to the living cell. Certain portions of cells have an affinity for particular dyes. Thus the mitochondria are stained in the live cell by Janus green, nerve material by methylene blue, many cell granules by neutral red, certain connective tissue cells by Pyrrol or Trypan blue, etc. This gives a valuable method for classifying cells as well as for obtaining information with regard to their structure.

STRUCTURE OF THE CELL. In every cell can be distinguished the two parts—nucleus and cytoplasm. The nucleus is generally an oval or spherical body lying near the centre of the cell and bounded by a definite *nuclear membrane*. In its interior it contains masses or filaments of a material known as *chromatin*, which are strung, so to speak, on a fine network of material known as *linin*. Besides the granules of chromatin, other masses are sometimes found which stain in a different manner and are

called *nucleoli*. The material filling up the meshes of the network is the nuclear sap or *nucleoplasm*. The cytoplasm, which varies greatly in extent in different cells, varies also in its appearance, being sometimes homogeneous, sometimes alveolar, sometimes granular in structure. In it can be often distinguished differentiated parts which may be regarded as organs of the cell.

The most universal of these cell inclusions, or possibly cell organs, are the *mitochondria* or *chondriosomes*. These occur in the form of granules, rods or filaments in almost every type of cell, animal and vegetable (*cp.* Fig. 6). Their function is unknown, though they seem to be more numerous and longer in cells which are very active. They are often grouped at one pole of the cell; thus in gland cells they are frequently found at the pole nearest to the blood capillaries and furthest from the lumen. They are more abundant in young than in old cells, and in the living cell are seen to move about readily in the cytoplasm. When the cell divides the mitochondria are shared

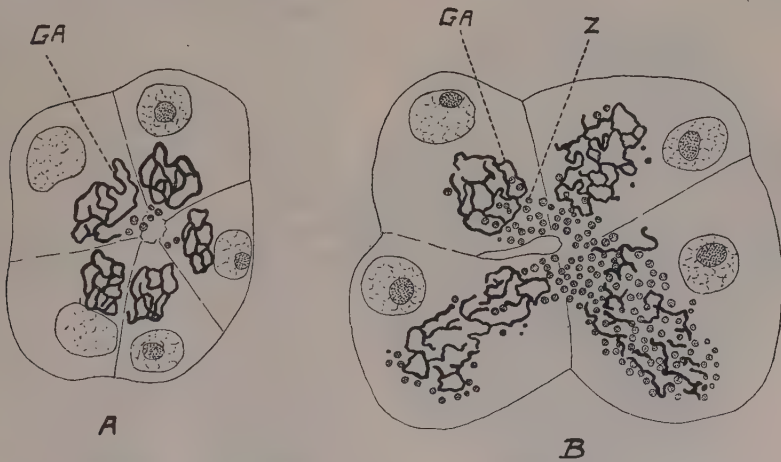


FIG. 7. Diagram of Golgi apparatus (GA) in secreting cells of the pancreas. A. In the contracted condition, after discharge and prior to re-formation of zymogen. B. Zymogen granules (Z) in relation to enlarged form of Golgi apparatus during active formation of zymogen. (LUDFORD.)

between the two daughter cells. In some conditions the mitochondria can be dragged out of the cell by microdissection methods, so that they are relatively solid. They consist of phospho-lipins in association with protein. Usually they are dissolved by alcohol and by weak acids, and so are not displayed in cells hardened with a view to display nuclear structure. In the living cell they can be stained with Janus green. They are best preserved by hardening in formalin and bichromate and staining with iron hæmatoxylin.

Another cell structure is the so-called *Golgi apparatus*, a reticular structure often located at one pole of the cell, soluble in alcohol, blackened by osmic acid and, after suitable fixation, stainable with silver salts (Fig. 7). In secretory cells it is usually found between the nucleus and the lumen. The functions of the Golgi apparatus are unknown, and some cytologists even deny their existence, claiming them to be artefacts produced by precipitation of lipides in presence of proteins. It has been suggested that certain products of cell activity, *e.g.* zymogen granules, can be assembled at the surface of the Golgi apparatus.

Special inclusions are also met with in certain cells, the best example being

the Nissl bodies of nerve cells. There seems little doubt that the actual particles of these substances are artefacts produced in the course of fixation. In addition to these cell organs the cytoplasm may contain visible *granules* of material of various types, which are usually formed by the activity of the cytoplasm or stored there until required. Thus we have granules of *zymogen* found in secreting cells and representing a precursor of the enzymes which the cell liberates during activity, or granules of food material provisionally stored in the cytoplasm until required, *e.g.* fat or glycogen.

THE PHYSICAL STRUCTURE OF PROTOPLASM. Owing to the close similarities which exist between the fundamental properties of all living organisms, histologists have sought to discover some corresponding uniform morphological organisation of the physical basis of these phenomena, namely, protoplasm.

It is often impossible, even under the highest powers of the microscope,

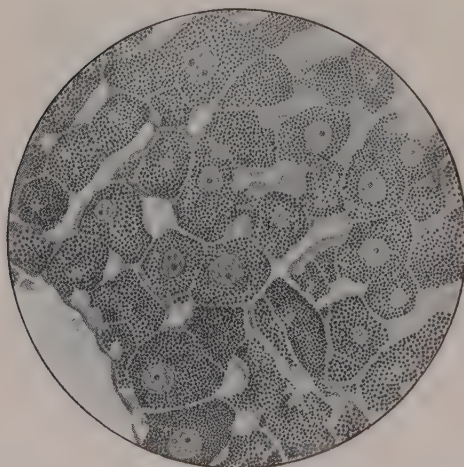


FIG. 8. Section of Liver stained to show Granules.
(ALTMANN.)

to make out any structure whatsoever in the cytoplasm, which is spoken of then as hyaline. In most cases examination of a cell, even unstained, shows some differentiation between a more or less regular framework or mesh-work and a more fluid portion filling up its interstices, and these appearances are still more manifest when the cells have been fixed by various hardening fluids. All the results obtained in this manner must be regarded with some suspicion, since, as has been shown by Fischer and by Hardy, it is possible to imitate artificially the various structures, which have been assigned as characteristic of protoplasm, by hardening a homogeneous

colloidal solution such as egg-white by different methods and with different reagents. Thus the theories of protoplasmic structure, which have been put forward as the result of observations on hardened tissues, possess little more than historic interest.

The following are the chief theories :

(1) **The Granular Theory of Altmann.** By the use of certain hardening reagents, a dense mass of spherical or rod-shaped granules may be demonstrated in almost all cells of the body (Fig. 8). It is probable that many different kinds of structures of varying importance are included among Altmann's granules. In many cases they fall into the group of mitochondria.

(2) **The Fibrillar Theory.** By the employment of appropriate methods of hardening, it is easy in most cells to demonstrate a network or clusters of fibrils which form, so to speak, a denser part of the cell. This fibrillar network has been named the '*spongioplasm*' in contradistinction to the structureless material filling its meshes known as '*hyaloplasm*.' It is probable that in most cases the network which is seen in hardened cells is simply an artefact. Sometimes a large portion of the protoplasm may take a fibrillar form which can be detected even in the unstained and unfixed cell, and there is no doubt that, in certain phases at any rate, the fibrillar structure of the protoplasm is really present.

(3) **The Alveolar Theory of Bütschli.** If we imagine a hyaline protoplasm

which is continually manufacturing metaplasmic products and storing them up in its protoplasm, these products will be deposited as spherules gradually increasing in size, so that the protoplasm between them will be converted into alveolar partitions between the droplets. In many an egg cell, where there is a growth of protoplasm from this building up of food into reserve materials, the development of such an alveolar structure can be followed in the living protoplasm, and such cells when mature show a marked alveolar structure whether examined fresh or in the hardened and stained condition. Such a protoplasm would be practically an emulsion of one fluid in another and, according to Bütschli, artificial emulsions, made by mixing rancid oil with sodium carbonate solutions, may show under the microscope a very close resemblance to cell protoplasm (Fig. 9), and may even exhibit amœboid changes of form in consequence of the diffusion currents set up at the surface of the drop between its contents and the surrounding water.

Most histologists are in accord that none of the above theories can be regarded as applicable to all forms of protoplasm, but that during the life of a cell its protoplasm, as observed under the microscope, may be either hyaline and structureless or may present any of the structural modifications described above, according to its state of nutrition and the form in which its metabolic products are laid down in the cell. Of course it is possible that, even in the apparently hyaline protoplasm, a structural differentiation is still present, but is invisible owing to the minute size of its constituent parts or an identity of refractive index between the alveolar walls and their contents. The fact that every chemical differentiation occurring within the colloidal mass will tend to cause differences of surface tension, and therefore formation of droplets, shows that an alveolar structure, *i.e.* one in which there is a large number of surfaces separating heterogeneous mixtures inside the cells, must be of very common occurrence, even in cases where it is not detectable under the microscope. Such a structure must be present, at any rate, in those cases where, apart from the existence of a solid cell wall, the cell presents a certain degree of rigidity and resistance to deforming stress.

ULTRAMICROSCOPIC STRUCTURE OF PROTOPLASM.

Since the study of the behaviour of the cell shows that it must possess a much more complex structure or organisation than that which is revealed by the microscope, one, that is to say, which permits of the spatial differentiation of the different chemical processes that may occur at one and the same time in the protoplasm, many theories have been put forward of an ultramicroscopic cell structure.

The first elaborate conception of such a structure was worked out by Nägeli (1884). According to Nägeli all organised structures are made up of micellæ, minute particles arranged in definite order and surrounded with water. The vital properties of the protoplasm were regarded as the sum of the changes taking place in the individual micellæ. Similar conceptions have been put forward by numerous other observers.

Ultramicroscopic examination of living cells certainly shows that the cytoplasm is crowded with granules of various sizes, even though it may appear homogeneous to ordinary microscopic observation. These granules are able to move about within the cell, and indeed, in certain cases, display a lively Brownian movement. In most animal cells, however, the cytoplasm appears to be too viscous to allow of very active movement of this description, and this view of the viscous though fluid nature of protoplasm

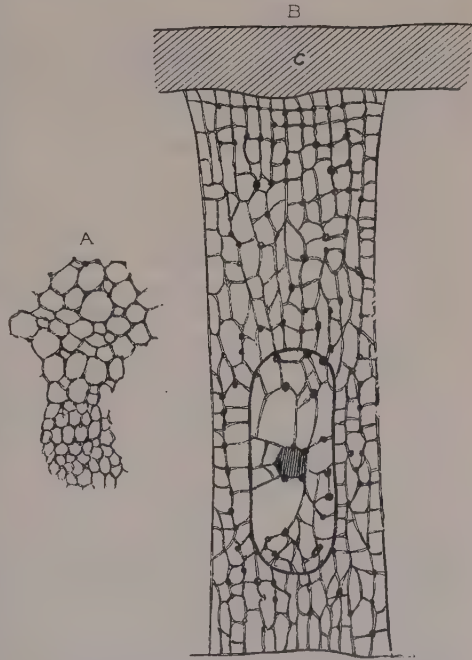


FIG. 9. A, Foam-like Appearance of an Emulsion of Olive Oil; B, Protoplasm of an Epidermal Cell of the Crayfish. (BÜTSCHLI.)

is fully borne out by observations by micro-dissection. It is certain, therefore, that cytoplasm is of a colloidal and heterogeneous structure.

One question which has been much discussed relates to the physical condition of protoplasm. Is it to be regarded as a viscous fluid or as a soft solid? The perfect potential mobility of the protoplasm of many cells, as instanced by the flow of the substance of an amœba into its pseudopodia, or the occurrence of rapid streaming movements in the threads of protoplasm found in many plants, *e.g.* the root hairs of tradescantia, or the ready movements of granules or mitochondria within animal cells in tissue culture, indicates a fluid character for the protoplasm. This view is supported by the observation that when small amounts of water are injected into the substance of a cell the water at once mixes freely with the cytoplasm. Against such a character has been urged the fact that in protoplasm we may have shape, organisation, and power of resistance to deformation—qualities which are generally associated with the possession of solidity. It must be remembered, however, that the absence of resistance to deformation which is characteristic of a liquid, applies only to the internal molecules, and that the surface of any liquid is in a condition of tension which not only limits deformation but presents considerable resistance to any enlargement of the surface. The continued existence of protoplasm in a watery environment shows that not only must its composition be different from that of its environment, but that there must be a distinct surface separating the two. The superficial layers of the protoplasm must therefore be in a condition of tension, and exercise pressure on the internal portions of the cell, which will tend to bring it into the spherical form.

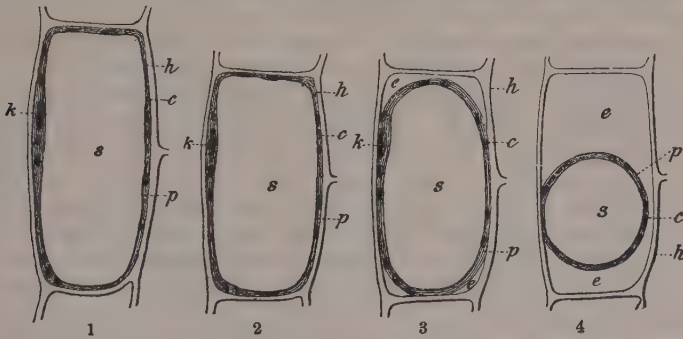
The smaller the mass of protoplasm, supposing it to be homogeneous, the greater will be the pressure exerted by its surface layer on its contents and the greater resistance will it present to deformation of the spherical form. A fluid drop, if suspended in a fluid with which it is immiscible, will present greater rigidity the smaller its dimensions. Almost any degree of rigidity can thus be imparted to an emulsion. In such a case every droplet will present resistance to deformation and every surface will resist penetration or extension. The resistance of the surface in colloidal fluids is still further increased by a property common to all these fluids, namely, the aggregation in the surface layer of a greater concentration of the dissolved substance than is present in the underlying fluid. If for instance we take a beaker containing egg-white diluted 100 times, and drop a steel magnetised needle on to the surface, it will float although it is much heavier than the fluid, in consequence of the resistance of the surface. If the needle be greasy the same thing will occur on a glass of water. In this case the needle will lie N. and S. On the albumin solution, however, the needle will lie in the position in which it has been dropped. The aggregation of the albumin molecules on the surface of the fluid results in the formation of a solid film which resists any turning of the needle. What applies to the interfacial surface between fluid and air applies also to that between two different fluids. Thus in milk, which is an emulsion of fat droplets in a protein solution, each droplet of fat is surrounded by a layer of concentrated, possibly solid, protein. Protoplasm may be regarded as essentially fluid in character, the form and rigidity which are acquired by most cells being due to physical differentiation occurring in its substance, as when the colloid is a stiff emulsion, or when, as at the surface, there is the formation of a solid condensation layer. The physical condition of protoplasm is without doubt subject to considerable and often very sudden changes. When, for instance, a living cell is damaged by a micro-dissection needle, the fluid homogeneous cytoplasm almost at once sets to a

jelly-like semi-solid, in which definite granules soon appear. Bayliss showed that when an amoeba was stimulated electrically, while observed by dark-ground illumination, the fine movement of the granules was momentarily checked, also presumably owing to a temporary solidification of the cytoplasm.

THE SURFACE LAYER OF CELLS. Since it is by means of its surface layer that the organism enters into relation with its environment, this layer acquires a prime importance for the life of the cell, and we may therefore consider here at greater length some of the properties of this layer, the *Plasma membrane*, as it has been called.

The superficial layer of the protoplasm is not to be confounded with the cell wall of plant cells, which is generally freely permeable to all kinds of solutions, and so plays no part in regulating the interchanges of the cell with the environment.

The superficial layer of protoplasm represents that part of the living substance which stands in immediate relationship to the environment. Every change in the latter can influence the living cell only through this layer, and it is through this layer that substances must pass on their way into



. FIG. 10. Vegetable Cells, showing varying degrees of Plasmolysis. (DE VRIES.)

the cell for assimilation, or out of the cell for excretion. The retention of an individuality by the cell must be determined by chemical and physical differences between this layer and the surrounding fluid. Since it differs from the rest of the protoplasm in the changes to which it is subject, it must also differ in its chemical composition, apart altogether from the factors which, as we saw above, determine molecular differences between the surface and the interior of any colloidal solution. On this account one must assume the existence of a definite boundary layer of the protoplasm, even where it is impossible to see any differentiation between this layer and the deeper parts under the highest powers of the microscope.

A living cell, which leads its life in a liquid environment, must take up the greater part of its food material in the form of solution; and it is the permeability of the superficial protoplasm which will determine the passage of food substances from the surrounding medium into the body of the cell. The immiscibility of the protoplasm with the surrounding fluid shows that the permeability of the membrane must be a limited one. The qualitative permeability was first studied in vegetable cells. These present within a cellulose wall a thin layer of protoplasm (the 'primordial utricle'), enclosing a cell sap. If the root hairs of *Tradescantia* be immersed in a 10 per cent. solution of glucose or in a 2 to 3 per cent. solution of salt, a process of *plasmolysis* takes place. The cell sap diminishes in amount by the diffusion

of water outwards so that the primordial utricle shrinks (Fig. 10). On placing the cells in distilled water, water passes into the cell sap until the further expansion of the protoplasmic layer is prevented by the tension of the surrounding cell walls. This behaviour can be explained only on the assumption that the protoplasm is impermeable both to sugar and to salt, but is freely permeable to molecules of water, *i.e.* it behaves as a semi-permeable membrane. Similar experiments can be made on red blood corpuscles. These also shrink when immersed in salt solutions with a greater molecular concentration than would correspond to the plasma of the blood from which the corpuscles were derived, whereas if placed in weak salt solutions or distilled water they swell up and burst, discharging their hæmoglobin in solution into the surrounding fluid (Hæmolysis). By comparison of various salts it is found that the strength of each salt solution which is just necessary to cause plasmolysis or hæmolysis, as the case may be, is determined entirely by its molecular concentration, *i.e.* a decinormal solution of sodium chloride will be equivalent in its effect on the cells to a decinormal solution of potassium nitrate or of potassium chloride. The limited permeability of the plasma membrane also enables the cell to maintain a different reaction, usually more acid than that of its surroundings. Most cells show a cytoplasmic pH of about 6.8 to 7.0 when tested by micro-injection of indicator dyes; the nucleus, which again is separated from the cytoplasm by a membrane, usually has a pH definitely higher (more alkaline), *viz.* about 7.6 to 7.8, according to micro-injection experiments by Chambers and Pollack. The impermeability of the plasma membrane does not apply to all dissolved substances. Overton has found that, whereas this layer is practically impermeable to salts, sugars and amino-acids, it permits the easy passage of monatomic alcohols, aldehydes, alkaloids, &c. All these substances are more soluble in ether, oil and similar media than they are in water. The passage of dissolved substances through a membrane wetted by the solvent depends on the solubility of these substances in the membrane; and Overton therefore concludes that the superficial layer of protoplasmic cells must itself partake of a 'lipoid' character, and that cholesterol and lecithin probably enter largely into its composition. He states that only such aniline dyes as are soluble in a mixture of melted lecithin and cholesterol have the property of penetrating the living cell, and only these dyes, such as methylene blue, and neutral red, can be used for *intra vitam* staining. This does not apply, however, universally. The kidney cells can take up many dyes which are not 'lipoid-soluble,' such as phenol sulphone-phthalein and indigo-carmin, and the same applies to other gland cells. It may be noted that substances which have the power of dissolving lecithin and cholesterol, such as ether or bile salts, also act as hæmolytic agents, *i.e.* they cause a destruction of the red blood cells by dissolving the superficial layer which is necessary for their preservation from the solvent effects of the surrounding fluid.

The semi-permeability of the plasma skin can be altered by changes in the saline concentration or other factors of the surrounding medium. Overton has shown that, whereas a 7 per cent. solution of saccharose produces plasmolysis in living cells, no plasmolysis is observed if they are treated with a solution containing 3 per cent. methyl alcohol *plus* 7 per cent. cane sugar. The superficial layer therefore is able to dissolve a mixture of methyl alcohol and cane sugar, although it has no solvent power on cane sugar in pure watery solutions. It is possible that, in order to serve the nutrient needs of the cells, more extensive changes may take place in the permeability of the surface layer under limited conditions of time and space. There is no

doubt for instance that glucose, to which the surface layer is apparently impermeable, can yet serve as a very efficient food for the cell; and one might ascribe the fact, that the cell assimilates only the food which it requires and no more, to such limited changes in permeability.

An important factor in the process of assimilation, at any rate by lowly organised cells, must be the relative solubility of the absorbed substances in the cell and its surrounding medium respectively. When a watery solution of iodine is shaken up with chloroform, the latter sinks to the bottom, carrying with it the greater part of the iodine. If a watery solution of an organic acid be shaken with ether, the latter fluid will extract the greater quantity of the acid. In no case will the extraction be complete, but there will be a definite ratio between the amount dissolved by the ether and the amount dissolved by the water, the so-called 'partition coefficient,' depending on the different solubilities of the dissolved substance in the two menstrua. In the same way a mass of protoplasm will tend to absorb from the surrounding medium and to concentrate in itself all those substances which are more soluble in the colloidal system of the protoplasm than in the surrounding fluid; and this process of absorption may be carried to a very large extent, if the dissolved substances meet in the cell with any products of protoplasmic activity with which they form insoluble compounds so that they are removed from the sphere of action. It is probably by such a process as this that we may account for the accumulation of calcium or silicon in such large quantities in connection with the bodies of various minute organisms.

One hypothesis for explaining variations in permeability of cell membranes is that which regards the change as due to a *reversal of colloid phases*. A membrane of an emulsoid structure may consist of droplets of oil (disperse phase) in a watery medium (continuous phase), and so be permeable to watery fluids, or the phases may be reversed so that we get watery droplets in an oily medium, in which case only oil-soluble materials would pass through. Alteration of phase conditions often depends upon the inorganic ions which are present; thus calcium favours the dispersion of water in oil, and sodium that of oil in water.

Whereas assimilation by a living cell is ultimately conditioned by the permeability of the surface protoplasm, its form is determined by the tension of this layer. If the tension is uniform at all parts of the surface the form of the cell will be spherical. Any diminution of the surface tension at one point must tend to cause a bulging of the fluid contents at this point, just as on distending a rubber tube with one weak spot in its wall, this suddenly gives way with the production of a large balloon, which rapidly extends in size and ruptures unless the pressure be diminished. Diminution of the surface tension at one point of the cell will be attended by a contraction of all the rest of the surface and a driving out of the contents through the weak part. This process will not as a rule result in destruction of the cell; the resulting protrusion will be limited by the distortion of the internal alveolar structure of the protoplasm caused by any alteration of the spherical form of the cell. Change of form in living structures thus depends ultimately on alterations in surface tension, return to normal being effected by the elastic reaction of the structural arrangement of the protoplasm. This point we shall have to consider more fully when dealing with muscular contraction. At present it is sufficient to see how any slight alteration in the chemical environment, such as might be due to the presence of a particle of foodstuff, may cause local variations in the surface tension of the plasma skin and thus result in the protrusion of pseudopodia and the ingestion of the food particle.

Experiments carried out by micro-dissection methods with living cells show that when the surface of a cell is torn or punctured, or even when part of the cell is cut away, the surface film is often at once reformed. It thus appears to be in many cases a condensation layer formed at the surface of separation in accordance with the laws of surface tension. The presence of calcium appears to be essential for the formation of this membrane.

THE RELATIONS OF THE NUCLEUS TO THE CYTOPLASM.

The universal existence in living cells of a differentiated nucleus indicates that the life cycle of assimilation and dissimulation must depend on an interaction between the nucleus and cytoplasm, and that each plays a distinct part in the sum of the changes which make up the life of the cell. The different staining reactions of nucleus and cytoplasm, and the fact that the nucleus is more opaque to ultra-violet light, suggest a corresponding difference in their chemical composition, a suggestion which is confirmed by analysis. In the building up of protoplasm proteins play an important part. They are not

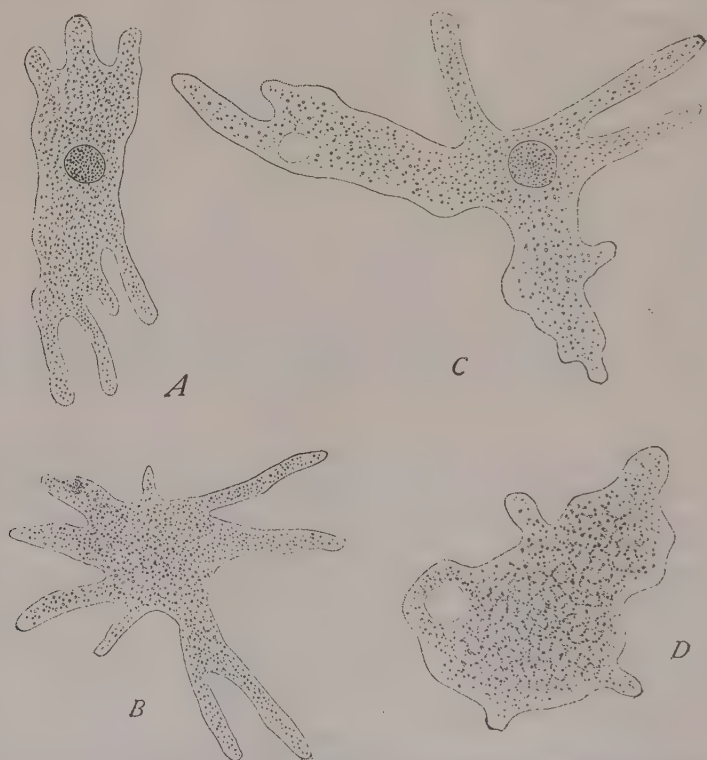


FIG. 11. Nucleated and Non-nucleated Fragments of *Amœba*. (WILSON after HOEFER.)

A, B. An *Amœba* divided into nucleated and non-nucleated halves, five minutes after the operation.

C, D. The two halves after eight days, each containing a contractile vacuole.

always present, however, as simple proteins, but are often built up with other complex bodies to form conjugated proteins. Whereas in the cytoplasm these conjugated proteins consist chiefly of compounds of protein and lecithin, in the nucleus the chief constituents belong to the class of nucleo-proteins. The nucleo-proteins are of varying composition, and are distinguished chiefly by the large amount of phosphorus in their molecule. A nucleo-protein can be broken down into nuclein and protein. Nuclein can be broken down into nucleic acid and a basic protein. Nucleo-protein seems to be the essential constituent of cell nuclei and to be present in only small quantities in the cytoplasm. The readily stainable material of the nucleus, called *chromatin* by histologists, consists mainly of nucleo-protein. It can be distinguished from other stainable cell contents by Feulgen's "nucleal" reaction. This test is carried out by treating sections with warm dilute hydrochloric acid

for a few minutes, transferring to fuchsin-sulphurous acid (Schiff's reagent) and washing in dilute sulphurous acid. Chromatin is stained violet owing to the presence of hexoses in the animal nucleic acid. The consistency of the nucleus is found on micro-dissection to be more solid than the cytoplasm, and it is seen in the resting live cell to be nearly homogeneous, except for the presence of nucleoli. When punctured it rapidly coagulates, and then there often appear, especially in cells about to divide, the characteristic chromatin filaments. These filaments can be drawn out like elastic by the needle, and retract again when released.

In order to appreciate the part played by the nucleus in the ordinary cell processes, we must study the behaviour of cells or parts of cells deprived of a nucleus and compare it with that of similar cells or parts of cells

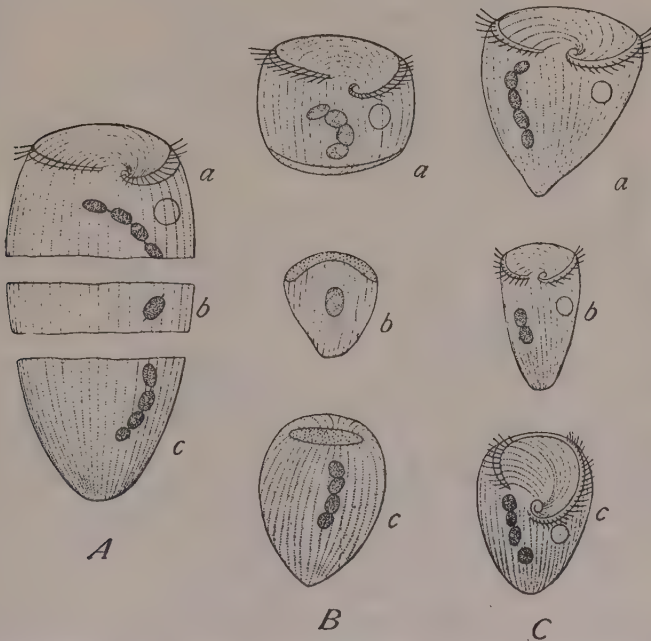


FIG. 12. Regeneration in the Unicellular Animal *Stentor*. (From GRUBER after BALBIANI.)

A. Animal divided into three pieces, each containing a fragment of the nucleus.

B. The three fragments shortly afterwards.

C. The three fragments after twenty-four hours, each regenerated to a perfect animal.

still containing a nucleus. By micro-dissection it is possible to divide the larger protozoa into two pieces, one with and one without a nucleus. Hofer, experimenting on the amoeba, found that the fragment containing the nucleus quickly regenerated the missing part and pursued a normal existence. On the other hand, the non-nucleated fragments showed no signs of regeneration. They might indeed live as long as fourteen days after the operation (Fig. 11). Their movements continued for a short time and then ceased, though the pulsations of the contractile vesicle were but little affected. The power of digestion of food was completely lost. Other observers have shown that *Stentor*, an infusorium which possesses a fragmented nucleus, may be broken up into fragments of all sizes. Nucleated portions as small as one-twenty-seventh the volume of the entire animal are still capable of regeneration. The wound quickly heals and the special organs—the mouth with its surrounding cilia, and the contractile vacuole—are regenerated, but all non-

nucleated fragments quickly perish (Fig. 12). In ciliated mammalian cells, the ciliary movement ceases when the nucleus is destroyed or removed.

Many similar observations have shown that the non-nucleated cytoplasm, though it may survive for some time and perform normal movements in response to stimuli, such as those of ingestion of food particles, loses entirely the powers of digestion, secretion and growth. In animals possessing a shell, a small secretion of the lime salts may occur on the surface, but this process rapidly comes to an end as the store of material in the cytoplasm is exhausted.

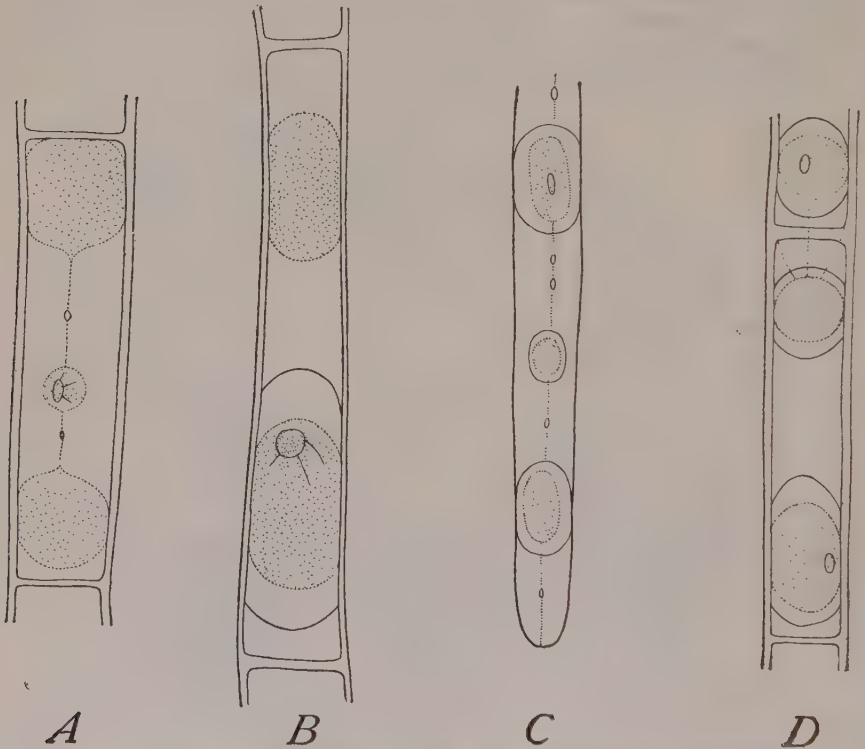


FIG. 13. Formation of Membranes by Protoplasmic Fragments of Plasmolysed Cells. (WILSON after TOWNSEND.)

- A. Plasmolysed cell, leaf hair of *Cucurbita*, showing protoplasmic balls connected by strands.
- B. Calyx hair of *Gaillardia*; nucleated fragment with membrane, non-nucleated one naked.
- C. Root hair of *Marchantia*; all the fragments, connected by protoplasmic strands, have formed membranes.
- D. Leaf hair of *Cucurbita*; non-nucleated fragment, with membrane, connected with nucleated fragment of adjoining cell.

In vegetable cells it is possible to break up the protoplasm by means of plasmolysis into nucleated and non-nucleated parts. The nucleated part quickly forms a new cell wall. The non-nucleated part is unable to effect this formation, and soon dies unless it is in connection with an adjacent cell containing a nucleus by means of fine threads of protoplasm which pass through pores in the intercellular septa (Fig. 13). In such animal cells as are connected together by protoplasmic bridges, e.g. the cells of the dermis, this does not seem to hold good, for Chambers found that when one of the cells in the mass was damaged, the coagulative process spreads to neighbouring cells. In the higher animals we have, in the case of the nerve

cell, an example of the necessity of the nucleus for growth. Here division of the nerve fibre causes degeneration of the whole fibre separated from the cell containing the nucleus; and regeneration of the fibre, when it occurs, is effected by a downgrowth of that part of the fibre which is still in connection with the nucleus. All these facts show that the power of morphological as well as of chemical synthesis depends on the presence of a nucleus. On this account the nucleus, as we shall learn later on, must be regarded as the especial organ of inheritance (Chapter XLIV.). The transmission of the paternal qualities from one generation to the next is effected by the entrance simply of the nuclear material of the male cell, the spermatozoon,

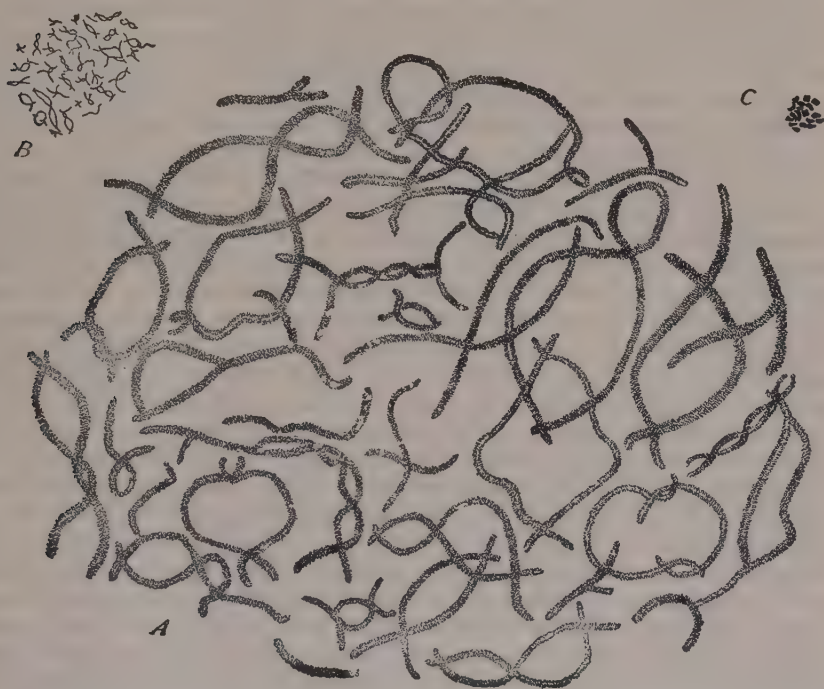


FIG. 14. Chromosomes of the Germinal Vesicle in the Shark *Pristiurus*, at different periods drawn to the same scale. (RÜCKERT.)

- A. At the period of maximal size and minimal staining capacity (egg 3 mm. in diameter).
 B. Later period (egg 13 mm. in diameter).
 C. At the close of ovarian life, of minimal size and maximal staining power.

into the ovum. In the words of Claude Bernard, "the functional phenomena in which there is expenditure of energy have their seat in the protoplasm of the cell (*i.e.* the cytoplasm). The nucleus is an apparatus for organic synthesis, an instrument of production, the germ of the cell."

Similar conclusions may be drawn from a study of the changes in the nucleus which accompany different phases in the activity of the whole cell. Thus in growing plant cells the nucleus is always situated at the point of most rapid growth. When this growth is finished the nucleus moves to another part of the cell. The active growth of cytoplasm, which accompanies the activity of secreting cells, is always associated with changes in the position and in the size of the nucleus.

The important changes which the nucleus undergoes in the process of

cell division we shall have to consider more fully in the later chapters of this work (Chapter XLV.). In the function of assimilation it is natural to assume that it is those constituents of the nucleus which are peculiar to it both morphologically and chemically, namely, the chromatin filaments, which are most directly concerned. This assumption receives support from the changes which have been observed to occur in these filaments during various phases of nutritive activity of the cell. The staining powers of chromatin are in direction proportion to the amount of nuclein it contains. In the eggs of the shark it has been shown that the chromosomes undergo characteristic changes during the entire growing period of the egg. At first they are small and stain deeply with ordinary nuclear dyes, but during the period of growth they undergo a great increase in size and at the same time lose their staining capacity, their surface being increased by the development of long threads which grow out in every direction from the central axis. As the egg approaches its full size, the chromosomes diminish in size and are finally reduced to minute intensely staining bodies which take part in the first division of the egg preparatory to its fertilisation (Fig. 14).

HISTOLOGICAL DIFFERENTIATION OF CELLS. Even within the limits of a single cell, differentiation of structure can take place by the setting apart of distinct portions of the cell for isolated functions. Thus in an organism such as vorticella the cell is shaped somewhat like a wine-glass, the stem being composed of a spiral contractile fibre which has the function of withdrawing the rest of the organism when necessary towards its point of attachment. The main portion of the cell presents at its free extremity a part which is the seat of ingestion of food, and is therefore spoken of as the 'mouth.' This is surrounded by a circle of cilia whose function it is to set up currents in the surrounding fluid and so favour the passage of food particles towards the mouth. Food when ingested at this end passes only a short distance into the body of the vorticella. Here fluid is secreted around it which serves for its digestion. This portion of the cell may therefore be regarded as the alimentary canal or stomach. The indigestible residue of the food is excreted in close proximity to the mouth. In addition to these organs we have the usual differentiation of the protoplasm into an external and internal layer, and the development within the protoplasm of contractile vacuoles, which serve to keep up a circulation of fluid and therefore to pass the products of digestion through all parts of the cell body. Within the limits of the single cell which forms the vorticella, we may therefore speak of organs for movement, for digestion, for circulation, and so on.

The organs which are thus formed in unicellular animals or plants can be divided into two classes, namely (1) temporary organs, which are formed out of a common structural basis and can therefore be replaced at any time by the cytoplasm if destroyed. Examples of such organs are the cilia, the commonest motor apparatus of unicellular organisms; the pseudopodia which, as we have seen, can be made and destroyed at will; the mouth of animals such as volvox or vorticella; and the stinging cells or nectocysts, which surround the mouth of many of these animals and serve to paralyse or kill the smaller living organisms brought by the cilia within reach in order that they may serve as food. In contradistinction to these organs are (2) a number of others which must be regarded as permanent. These cannot be formed by differentiation from the cytoplasm of the cell, but are derived by the division of pre-existing organs of the same character, and are therefore transmitted from one generation to another. As examples of such cell organs may perhaps be mentioned the nucleus with its chromosomes, and the mitochondria and plastids, of which the chloroplasts of vegetable cells are the most conspicuous. Certain cell organs may fall into either class. Thus the contractile vacuoles are sometimes derived by the division of the pre-existing vacuoles in a previous generation, at other times are certainly formed out of the common cytoplasm. The centrosome, a small particle generally situated in the cytoplasm, which plays an important part in cell division, is generally derived by the division of a pre-

existing centrosome, but under certain conditions and in some organisms can be developed *in situ* in the cytoplasm itself.

The possibility of histological differentiation and of the adaptation of structure to definite functions becomes much more pronounced as we pass from the unicellular to the multicellular organisms or metazoa. The lowest of the Metazoa, such as the sponges, consist of little more than an aggregation or colony of cells. All the cells are still bathed with the outer fluid, and any differentiation of structure or function seems to be entirely conditioned by the position of the cell. In the Coelenterata the differentiation is already much more marked. The hydra, one of the simplest of the group, consists of a sac formed of two layers of cells and attached by a stalk to some firm basis. Round the mouth of the sac is a circle of tentacles. The inner layer, or hypoblast, represents the digestive and assimilatory layer, while the epiblast, or outer layer, is modified for the purposes of protection, of reception of stimuli, and of motor reaction. In the jelly-fish the differentiation of the outer layers leads to the formation of the first trace of a nervous system, *i.e.* a system fitted especially for the reception of stimuli and for their transmission to the reactive tissues, namely, the muscles.

In all these classes of animals the external medium of every cell forming the organism is the sea-water or other medium in which they live. This can penetrate through the interstices between the cells, and every cell is therefore exposed to all the possible variations which may occur in the composition of the surrounding medium. A great step in evolution was accomplished with the formation of the Coelomata, the class to which all the higher animals belong. In these, by the formation of a body cavity containing fluid, an internal medium is provided for all the working cells of the body. The composition of this internal medium is maintained constant by the activity of the cells in contact with it, and the stress of sudden changes in the chemical composition of the surrounding medium is borne entirely by the outer protective layer of epiblast cells. These are rendered more or less impermeable by the secretion on their surfaces of a cuticular layer, and only such of the constituents of the surrounding medium are allowed to enter the organism as can be utilised by it for building up its living protoplasm. Out of the coelom is later on formed a circulatory system which, by the circulation of the coelomic fluid or of blood through the whole body, can procure a still more perfect uniformity in the chemical conditions to which every cell is exposed. It is not till much later that the organism achieves an independence of external conditions of temperature. In the Mammalia, by means of the reactive nervous system, the heat produced in every vital activity by the chemical changes of combustion and disintegration is so balanced against the heat lost through the external surface to the environment that the temperature of the internal fluid is maintained practically constant. One of the main results of the differentiation of function and structure is therefore a gradual setting free of the majority of the cells of the body from the influence of variations in the environment; and in the highest type of all animals, in man, this independence of external conditions is carried to a much further extent by conscious adaptations, such as the use of clothes, dwellings, artificial heating, and so on.

The differentiation of the cells, which compose the organs of the body, is determined in the first place by the different conditions to which they are exposed in virtue of their positions in the course of development. All the higher animals may be considered as built in the form of a tube, the external surface of which is modified for the purpose of defence and for adaptation to changes in the environment. From this layer there are developed not only

the protective cuticle, but also the organs of motor reaction, namely, the special senses and the nervous system. The internal surface of the tube is modified for purposes of alimentation. From it are developed all those structures which serve for the digestion of the foodstuffs, for their absorption into the common circulating fluid, for their elaboration after absorption, and their preparation for utilisation by other cells of the body. Between these two surfaces are situated the supporting tissues of the body as well as the organs for the conversion of the potential energy of the body into motion and work, namely, the muscles. Here also is the coelom, represented in the higher animals by the pleural, pericardial and peritoneal cavities. The alimentary canal projects for a considerable part of its course into this coelom, being attached to the body wall only by one side. From the coelom is also developed the blood vascular system, surrounded by contractile and connective tissue cells, which maintains a constant circulation of the blood throughout the body. By this differentiation the body becomes divided into a number of organs, each of which is composed of like cells, modified for a common function and bound together by connective tissue, the latter serving also to carry the blood vessels which convey the common medium for the working cells. In the study of physiology our task consists firstly, in the description of the special part taken by each organ in the general functions of the body, and secondly, in the determination of the limiting conditions of such functions and of the physical and chemical factors which they involve. Finally, we have to endeavour to form a complete conception of the chain of events concerned in the discharge of each function and of their causal nexus.

In the foregoing lines we have compared the higher animal to a colony of cells, and we often speak of an isolated cell of the body as if it were an independent elementary organism. A better term for such an aggregation of cells as presented by the higher animals is not however 'cell colony,' but 'cell state,' since, just as in the state politic, no cell is independent of the activities of the others, but the autonomy of each is merged into the life of the whole. With increasing differentiation there is increasing division of function among the various members of the state, and each becomes less and less fitted for an independent existence or for the discharge of all its vital functions. The more highly civilised a man becomes and the greater his specialisation in the work of the community, the smaller chance would he have of existing on a desert island. Thus the life of the organism is essentially composed of and determined by the reciprocal actions of the single elementary parts. It is evident that, if the process of specialisation has gone far enough, a discussion whether each unit has or has not an independent life is beside the mark, since it cannot possibly exist apart from the activities of the other cells. Of late years histologists have brought forward evidence which seems to imply that an actual structural interaction exists, in addition to the functional dependence which is a necessary result of specialisation. Even in the case of plant cells with their thick cellulose walls, fine bridges of protoplasm can be made out passing from one cell to another through pores in the cellulose wall. In animals protoplasmic bridges are known to exist joining up adjacent cells in unstriated muscle, epithelium and cartilage cells, and in some nerve cells. The conclusion has therefore been drawn that the morphological unit is not the cell but the whole organism, and that the division of the common cytoplasm into cells is merely a question of size and convenience. There can be no doubt that the determining factor in the division of cells is their growth: the cell divides because it grows. With increased mass of living substance it is necessary to provide for increase of

surface both of cytoplasm and of nucleus. Whether all the tissues of the higher animals remain in structural continuity by protoplasmic bridges, &c., must be a matter of indifference, since all that is necessary for the interdependent working of the different cells of the body is a functional continuity, and this in the higher animals is effected by the presence of a common circulating fluid and a reactive nervous system connected by conducting strands with all the cells of the body.

THE MATERIAL BASIS OF THE BODY

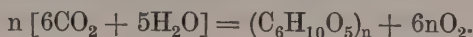
CHAPTER III

THE ELEMENTARY CONSTITUENTS OF PROTOPLASM

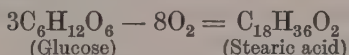
THE material basis of which living organisms are built up is derived from the surrounding medium, and the elements which compose the framework of the body must therefore be identical with those found in the earth's crust. Not all the elements are so utilised in the formation of living matter. Every living organism without exception contains the following elements: carbon, hydrogen, oxygen, nitrogen, sulphur, phosphorus, chlorine, potassium, sodium, calcium, magnesium, and iron. In addition to these twelve elements others are found in certain organisms, sometimes to a large extent, but it is not known how far they are necessary to the proper development of these organisms, and it is certain that they do not form an integral constituent of all organisms. Of these elements we may mention especially silicon, iodine, fluorine, bromine, aluminium, manganese, and copper. Dealing with the first class, which includes those essential to all forms of life, we find that their relative proportions in living organisms have little or no relation to their proportions in the environment of the organisms. Their presence however in the latter is a necessary condition of life. In the case of plants which have a fixed habitat and cannot move in search of food, the growth of the plant is limited by the amount of the necessary element which is present in smallest quantities in the surrounding medium. Of the elements derived from the earth's crust, those present in the smallest amounts in most soils are potassium, nitrogen, and phosphorus. The growth of a crop in any given soil is determined by the amount of that one of these three substances which is present in smallest quantities.

Carbon forms the greater part by weight of the solid constituents of living protoplasm. The proximate constituents of living organisms are practically all carbon compounds, so that organic chemistry, which was originally the chemistry of substances produced by the agency of living organisms, has come to be synonymous with the chemistry of carbon compounds. The carbon compounds which make up the living cell are combustible, *i.e.* they can unite with oxygen to form carbon dioxide with the evolution of heat. In the inorganic world practically all the carbon occurs in a completely oxidised form, namely, carbon dioxide, except for the coal, shale and petroleum deposits, which may be regarded as simply the *débris* of the organic world of bygone ages. A small amount, 1 part in 10,000, is present in the atmosphere, while vast quantities are buried in the crust of the earth as carbonates of the alkaline earths, &c., in the form of chalk and limestone. In this condition the carbon dioxide is practically removed from the life cycle, the whole of the carbon contained in the tissue of living beings, whether plant or animal, being derived from the minute proportion of carbon

dioxide present in the atmosphere. The energy for the conversion of carbon dioxide into the oxidisable forms with high potential energy, which make up the tissues of plants and animals, is furnished by the sun's rays. The conversion of the radiant energy into the potential chemical energy of the carbon compounds is performed by the chlorophyll corpuscles in the green parts of plants. In these corpuscles, under the influence of the sun's rays, the carbon dioxide of the atmosphere, together with water, is converted into carbohydrates, viz. starch $(C_6H_{10}O_5)_n$, and the oxygen liberated in the process is set free into the surrounding atmosphere.



In this process a large amount of energy is absorbed, but this can be set free later by the oxidation of the starch to carbon dioxide. In the oxidation of 1 gramme of starch about 4500 calories are evolved, and this represents therefore the measure of the solar energy which must be absorbed by the chlorophyll corpuscle in the process of formation of starch from carbon dioxide. By this means the world of life is provided with a source of energy. At the expense of the energy of the starch further synthetic processes are carried out. By the oxidation of a part of the carbohydrates, sufficient energy may be supplied to deoxidise other portions of the carbohydrates with the production of fats. Thus



The potential energy of a fat is still greater than that of a carbohydrate, 1 gramme of fat giving on complete combustion to carbonic acid and water as much as 9000 calories. By the introduction of ammonia groups (NH_2) into the molecules of fatty acids, amino-acids may be produced, from which the complex proteins are built up to form the chief constituents of the living protoplasm. The synthesis of carbon compounds from carbon dioxide is effected almost entirely by the chlorophyll of plants. A few micro-organisms, such as the sulphur bacteria, use the energy set free by the oxidation of sulphur compounds to sulphates for the process of carbon assimilation. Such organisms may be described as *chemo-synthetic*, as distinct from the photo-synthetic organisms comprising the green plants.

All animals take in carbon, hydrogen, nitrogen, oxygen and sulphur in the form of the carbohydrates, fats and proteins which have been built up in the living plants. In the animal organism these foodstuffs serve as sources of energy. They undergo a gradual oxidation, and finally leave the body in the form of carbon dioxide, water, ammonia or some related compound, and sulphates. A sharp distinction has therefore often been drawn between the metabolism of plants and animals, plants being regarded as essentially assimilatory in character while animals are dissimilatory, utilising the stores of energy which have been accumulated by the plant. There is however no definite line of demarcation. Although, generally speaking, the green plant breaks up carbon dioxide, giving off oxygen and storing up carbon compounds, and the animal taking in carbon compounds oxidises them with the help of the oxygen of the atmosphere to carbon dioxide, which is redischarged into the surrounding medium and is available for further assimilation by plants, yet this process of respiration is common to all living organisms, whether plants or animals. In the green plant it may be masked by the assimilatory process occurring under the influence of the sun's rays, but in the dark all parts of the plant, and in the light all parts which are free from chlorophyll, display a process of respiration, *i.e.* they are constantly taking up oxygen

from the atmosphere and using it for the oxidation of carbon compounds in their tissues, with the production of carbon dioxide.

The sum total of the processes of life tends therefore to maintain a constant proportion of carbon dioxide and oxygen in the atmosphere, the decomposition of carbon dioxide by the green plants being balanced by the oxidation of the carbon compounds and the continual discharge of carbon dioxide by animals. It is not certain however that this balance will be maintained throughout all time. As Bunge has pointed out, there are cosmic factors at work which are apparently tending to cause a constant diminution in the quantity of carbon dioxide in the atmosphere, which alone is of value to the plant.

Hydrogen exists almost exclusively in the form of water. In this form it is taken up by plants and animals, with the exception of a small proportion absorbed in ammonia. As water too it is discharged by living organisms.

Oxygen is the only element which, in all the higher organisms at any rate, is taken up in the free as well as in the combined state. It forms one-fifth of the atmosphere and, as the oxides of the various metals, a considerable fraction of the earth's crust. It takes a position apart from the other foodstuffs in that its presence is the essential condition for the utilisation of their potential energy. In the living cells it combines with the oxidisable compounds formed by the agency of the living protoplasm, with the production of carbon dioxide and water and the evolution of energy. This process is spoken of as respiration.

Like the three elements we have already considered, *nitrogen* is also derived directly or indirectly from the surrounding atmosphere. Very little nitrogen is to be found in the combined state in the earth's crust, whereas it constitutes four-fifths of the atmospheric gases. It can be taken up by most plants only in the form of ammonia, nitrites or nitrates. Animals cannot utilise these compounds, and their only source of nitrogen is the protein which has been built up from them by the agency of the plant cell. Since nitrogen in the free state is useless to nearly all living organisms, the existence of life must depend on the amount of combined nitrogen which is available. There are certain cosmic factors which result in the production of combined nitrogen. Every thunderstorm results in the production of small quantities of ammonium nitrite, which will be washed down with the rain and serve as a source of combined nitrogen to the soil. Every decaying vegetable or animal tissue serves as a source of ammonia. These forms of combined nitrogen are not however suitable for all classes of plants. Most moulds can assimilate ammonia as ammonium carbonate or as amino-acids or amines, provided that they are supplied at the same time with sugar, the oxidation of which will serve them as a source of energy. Many of the higher plants require their nitrogen in the condition of nitrates, and this conversion is effected by a group of micro-organisms. There are a number of bacteria (*bacterium nitrosomonas*) which have the power of converting ammonia into nitrites. Others (*bacterium nitromonas*) convert nitrites into nitrates. If sewage matter rich in ammonia is allowed to percolate through a cylinder packed with coke and the process be continued for several weeks, it is found after a time that in its passage through the filter the fluid has lost its ammonia and contains the whole of its nitrogen in the form of nitrate. At the top of the cylinder the nitrous bacterium is present, in the bottom of the cylinder the nitrate bacterium is present. This has been made the basis of a method of treatment of sewage which is now very largely employed. These different bacteria play an important part in all soils in preparing them for the cultivation of crops.

Definite evidence is available that organisms exist which can also bring into combination the free atmospheric nitrogen itself. Thus certain soils have been found to undergo a gradual enriching in nitrogen although no nitrogenous manure has been applied to them. Winogradsky has shown that this fixation of nitrogen by soils is effected by a distinct micro-organism, which may be isolated by growing it on gelatinous silica free from any trace of combined nitrogen, so that the organism has to procure its entire nitrogen from the atmosphere. Under such conditions the numerous other micro-organisms of the soil die of nitrogen starvation, and only the microbe survives which is able to utilise free nitrogen. This organism, which he called *clostridium pasteurianum*, grows well on sugar solution if free from ammonia and enriches the solution with combined nitrogen. It is anaerobic, and in the soil, where oxygen is constantly present, it occurs associated with two species of bacteria which are aerobic and protect it from the surrounding oxygen.

In addition to this spontaneous fixation of nitrogen by humus, a method has long been known to farmers by which the fertility of a soil can be increased without the application of nitrogenous manures. The growth of almost any leguminous crop in a soil poor in nitrogen may result, not only in the production of a crop containing much combined nitrogen, but also in an actual increase of nitrogen in the soil from which the crop is taken. It was then pointed out that the power of a leguminous crop to enrich the soil with nitrogen was dependent on the presence on the roots of certain small nodules (Fig. 15), and that the production of these nodules took place only as a result of infection. Beans sown in sterilised sand produced a plant free from nodules, but which grew very feebly unless nitrogenous manure were added to the sand. If however the sterilised sand were treated with an infusion of root nodules from another plant without the addition of any combined nitrogen at all, the beans developed nodules on their roots and grew luxuriantly, and at the termination of their growth the soil was richer in nitrogen than at the commencement. On microscopic examination the protoplasm which makes up these nodules is found to be swarming with bacteria which can be cultivated in media apart altogether from the plant. We have thus an example of a class of bacteria which, like those of humus, are able to assimilate the free nitrogen of the atmosphere but, unlike them, can effect this assimilation only in a condition of symbiosis, *i.e.* living in the growing tissues of a leguminous plant. Similar nodules have been described on the roots of other plants which can grow in a soil free from combined nitrogen, *e.g.* conifers.

Sulphur is found in all soils in the form of sulphates, generally of lime. In the plant cell a process of deoxidation takes place, and it is built up, together with nitrogen, carbon and hydrogen, to form sulphur derivatives and amino-acids such as cystine, and these, together with other amino-acids, are synthesised to form proteins. Practically the whole of the sulphur taken in by animals is in the form of proteins. It shares the oxidation of the protein molecule in the animal body which it leaves in the form of sulphates. It is returned to the soil in the form in which it was taken by the plant, and the cycle can be continuously repeated.



FIG. 15. Root of Vetch with Nodules.

Iron, although forming but a minute proportion of the material basis of living organisms (the whole body of man contains only six grammes), is nevertheless indispensable for the maintenance of life. It is necessary for instance in two important functions, viz. the formation of chlorophyll in the green plant and the respiratory process in the higher animals. Although iron constitutes no part of the chlorophyll molecule, plants grown in the absence of this substance remain etiolated, but form chlorophyll if the smallest trace of iron is added to the soil in which they are growing or even if the leaves are washed with a very dilute solution of an iron salt. In animals iron forms an essential constituent of hæmoglobin, the red colouring matter of the blood, whose office it is to carry oxygen from the lungs to the tissues. The pigment chlorocruorin, present in the plasma of polychæte worms, is an iron compound resembling hæmoglobin. It is probable too that the minute traces of iron in protoplasm exercise an important function in the processes of oxidation which are continually going on. Iron is obtained by plants from the soil as ferrous or ferric salts. In the protoplasm it is built up into highly complex organic compounds, and in this form is taken up by animals. It is probable that the main requirements of the animal for iron, which are very small, may be satisfied entirely at the expense of these organic compounds, but there is little doubt that the animal can, if need be, also utilise the iron salts present in its food. The animal proceeds extremely economically with its supply of iron. Any excess of iron above that needed to supply the iron lost to the body is excreted almost entirely with the fæces in the form of sulphide. In the soil this undergoes oxidation and returns once more to the form in which it was originally taken up by the plant.

Phosphorus is absorbed by the plant as phosphates. In the cell protoplasm it is built up with fatty acids and other organic radicals to form complex compounds such as lecithin, a phosphorised fat, and nuclein, a combination of phosphorus with nitrogenous bases of great variety. Both lecithin and nuclein are essential constituents of living protoplasm. Practically the whole of the phosphorus income of animals is represented by these lecithin and nuclein compounds. After absorption into the animal body they are broken down by processes of dissociation and oxidation, with the production, as a final result, of phosphates which are excreted with the urine or fæces and return to the soil.

Chlorine, potassium, sodium, calcium and magnesium are taken up by the plants in the form of salts. Magnesium is one of the elements present in the chlorophyll of plants. Although playing an essential part in all vital processes, they do not seem to be built up into organic combination with the constituents of the cell protoplasm except as salts of the proteins. This association of certain elements with the acid and basic groups of the protoplasmic constituents plays a fundamental part in the physical chemistry of the cell, and therefore in the molecular changes associated with excitation, secretion and other vital manifestations. They are taken up by animals in the form of salts, and as such are again excreted with the urine.

Little is known about the significance, if any, of the other elements which I have mentioned as occasional constituents of living beings. *Silicon*, which is of universal distribution, is assimilated as silica, probably in colloidal solution, and is distributed in minute quantities through all plant and animal tissues. It forms a very large percentage of the mineral basis of grasses, but even here it does not seem to be indispensable, since these will grow in a medium devoid of silica as luxuriantly as under normal conditions.

Fluorine is found in the enamel of the teeth and in minute traces in other tissues of the body.

Bromine, though present in quantity in some seaweeds, appears to play no part in the economy of higher animals.

Iodine is found in large quantities in many seaweeds and is present as an organic iodine compound in the skeleton of certain horny sponges. The substance thyroxin, the active principle of the thyroid gland, contains iodine, and is essential for normal life in the higher animals. Iodine therefore would seem to be an essential constituent of the higher animals.

Aluminium is found in large quantities in certain lycopods. Whether it is essential to their growth is not known.

Copper is certainly not a necessary constituent of a large number of plants and animals. In the cephalopods and crustacea it appears to take the part of iron in the formation of a blood pigment, hæmocyannin, which plays the same part in the blood of these animals that is played by hæmoglobin in the blood of vertebrates. When oxidised it is of a blue colour, but gives off its oxygen and is reduced to a colourless compound on exposure to a vacuum.

Manganese is widely distributed in traces, and in the lamellibranch *Pinna squamosa* appears to form an essential constituent of a blood pigment, like hæmocyannin in its functions, and called pinnaglobulin.

Among these elementary constituents of the body, a definite line of demarcation can be drawn between the carbon and hydrogen on the one hand and all the other constituents on the other. The first two elements are built up in a deoxidised form into the living structure of the protoplasmic molecule. The products of their complete oxidation are volatile, namely, carbon dioxide and water, and leave the body in these forms. The nitrogen set free by the breaking down of the proteins passes off as free nitrogen or as ammonia. The sulphuric acid formed by the oxidation of the sulphur combines with the bases to form non-volatile salts. We may therefore divide the ultimate constituents of the body into those which are combustible and are driven off on heating, and those which are left behind as the ash.

THE MATERIAL BASIS OF THE BODY

CHAPTER IV

THE PROXIMATE CONSTITUENTS

IN spite of the enormous variety of the proximate constituents of living organisms, most of them are members or derivatives of three classes of compounds. Since living organisms form the chief food of the animal kingdom, a study of these proximate constituents includes the study of all the food-stuffs. These classes are :—

The Lipides, or Fats, containing C, H, O, and sometimes P and N.

The Carbohydrates, containing C, H, O, and occasionally N.

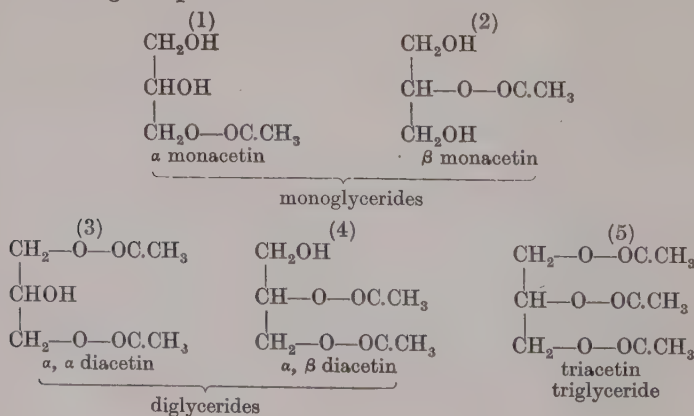
The Proteins, containing C, H, O, N, usually S, and occasionally P.

It is assumed that the student has some acquaintance with the elements of organic chemistry and with the properties of these compounds. We shall therefore confine our description here to those properties and reactions which have a direct bearing on the physiology of nutrition and metabolism.

1. THE LIPIDES

These substances are widely distributed throughout the animal and vegetable kingdoms. In the higher animals they are the main constituents of the fatty or adipose tissue lying under the skin and between the muscles, and often forming large accumulations around the viscera. In the marrow of bones they may account for 96 per cent. They also occur in fine particles in the protoplasm of cells and probably also in combination with the other constituents of protoplasm. Large amounts are also found in certain members of the vegetable kingdom, as for instance in the fatty seeds and nuts.

COMPOSITION OF THE FATS. The fats which form the chief representatives of simple lipides are esters of glycerol and the fatty acids. Glycerol is a trihydric or triatomic alcohol, and can therefore form esters (glycerides) with one, two or three of its hydroxyl groups. Thus with acetic acid the following compounds are known :

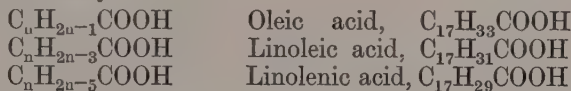


The glyceryl esters which compose the fatty material of living matter are mainly triglycerides, and natural fat is usually found to consist of various mixed triglycerides; these are not generally simple esters of the type shown in formula (5) but have different fatty acid radicals combined with the glycerol. The fatty acids which enter into the composition of the triglycerides may be either saturated or unsaturated, belonging to the homologous series having the following general formulæ :

Saturated fatty acids :

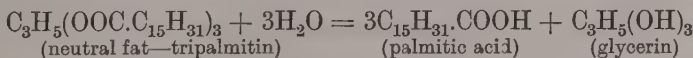


Unsaturated fatty acids :



In milk, although the greater part of the fat consists of the mixed glycerides of oleic, palmitic and stearic acids, other members of the series given above are present in small amounts. On the other hand, the adipose tissue, strictly so called, consists almost exclusively of the fats derived from the fatty acids, palmitic, stearic and oleic, *e.g.* dioleo stearin, oleo-palmito stearin, triolein, etc. The great differences in the appearance of the fat of different animals are due to the varying amounts in the relative quantities of these various fats which may be present. While triolein is liquid at 0° C., tristearin and tripalmitin are solid at the temperature of the body. According to the relative amounts of these three fatty acids therefore, we may have a fat which like mutton suet is solid at the body temperature, or a fat containing much olein which is still fluid and runs away when the body is opened after death, even when it has already cooled.

PROPERTIES OF THE FATS. The fats are colourless substances devoid of smell. They are insoluble in water, in which they float. They are soluble in warm absolute alcohol, but separate out into crystalline form on cooling. They are easily soluble in ether, petroleum ether, acetone, benzene and chloroform. If they are heated with water or steam or, more readily, with dilute mineral acids or with alkalis, or submitted to the action of certain enzymes, they undergo hydrolysis, taking up three molecules of water, and are split into three molecules of fatty acid and one molecule of glycerin, *e.g.* :



This process may occur spontaneously when fat is left exposed to the air. Fat which has been artificially split in this way is said to be rancid. Most natural fats generally contain a small amount of fatty acid which gives them an acid reaction.

On boiling a neutral fat for a long time with an aqueous or for a shorter time with an alcoholic solution of potassium or sodium hydrate, the fat, like other esters, undergoes saponification, giving the alkaline salt of a fatty acid and glycerin. The former compound is spoken of as a soap. In water the soaps form a sort of pseudo-solution on heating which sets to a solid jelly on cooling. From a dilute watery solution the soap can be thrown down in the solid form by the addition of neutral salts. An interesting phenomenon in connection with the digestion of fats is their *emulsification*. If a liquid fat be shaken with water, the droplets of fat become mechanically dispersed through the water, but quickly run together again on ceasing the agitation, so that the

mixture separates completely into two layers. If however alkali be added to the mixture until it is just alkaline to phenolphthalein—*i.e.* until the free fatty acids have been converted into soluble soaps—a fine creamy emulsion will then result from the shaking, and may remain stable for months. This is attributed to the stabilising effect of the soap upon the dispersed droplets of fat, due to the adsorption of the soap and its accumulation as a pellicle at the interface between water and each fat droplet, thus causing a corresponding reduction of the oil-water surface tension at the interface. The addition of acid, by precipitating the soaps as insoluble fatty acids, destroys this protective layer, and causes the immediate breakdown of the emulsion.

Owing to the difficulty which attends the complete separation of a mixture of allied fatty acids, such as is obtained by the hydrolysis of a fat, the complete analysis of a sample of a fat is seldom attempted, and in routine work a series of empirical determinations are made which together suffice to give a good deal of information as to the chemical nature of the fatty acids concerned. The following determinations are usual:—

The *melting point* and *refractive index*.

The *acid value* of a fat is the amount of potassium hydroxide in milligrammes required to neutralise the free fatty acids in 1 gramme of fat.

The *saponification value* is the amount of potassium hydroxide in milligrammes required to saponify 1 gramme of fat.

The *iodine value* is the amount of iodine in grammes absorbed by 100 grammes of fat.

The *Reichert-Wollny value* or *volatile fatty acid value* is the amount of N/10 potassium hydroxide in c.c. required to neutralise the volatile fatty acids in 5 grammes of hydrolysed fat.

The acid value gives an indication of the acidity or rancidity of the fat. The saponification value gives some idea of the mean molecular weight of the total fatty acids. The Reichert-Wollny value indicates the proportion of these which are volatile in steam (*i.e.* are of low molecular weight); and from the iodine value we can judge as to the degree of unsaturation of the acids of the fat. Certain other values in less general use provide information as to the amount of hydroxy-acids present, and the amount of unsaponifiable matter (cholesterol, &c.).

OTHER SIMPLE LIPIDES. Besides the glycerides, a certain number of substances occur in the body derived, not from a combination of fatty acids with glycerol, but from a formation of esters of the fatty acids with other alcohols, *e.g.* cholesterol or cetyl alcohol. Thus spermaceti is a mixture of cetyl palmitate with small quantities of other fats. The fatty secretion of the sebaceous glands in man and the higher animals, which furnishes the natural oil of hair, wool and feathers, consists of cholesterol esters with small traces of glycerides. Lanolin, which is purified wool fat, consists to a large extent of cholesteryl stearate and palmitate. These cholesterol fats are attacked with extreme difficulty by enzymes or micro-organisms. It is probably on this account that they are manufactured in the body for protective purposes. So far as we know, when once formed they are incapable of further transformation in the body. They are not appreciably altered by the digestive ferments of the alimentary canal, though cholesterol may be absorbed from the latter unaltered.* Cholesterol is also found in combination with fatty acids in every living cell. Whenever protoplasmic structures are extracted with boiling ether, a certain amount of cholesterol is present with the fats which are so extracted. In view of the great stability of this sub-

* According to Gardner, cholesterol may be absorbed from the intestine.

stance when exposed to the ordinary mechanisms of chemical change in the body, it seems probable that the part played by cholesterol is that of a framework or skeleton, in the interstices of which the more labile constituents of the protoplasm can undergo the constant cycle of changes which make up the phenomena of life. Cholesterol and its esters probably contribute materially to the surface conditions and permeabilities of protoplasm.

THE LIPIDES OF PROTOPLASM

The ether extract of a tissue contains not only the substances so far discussed, which should properly be called the simple lipides, but also other 'fat-like' compounds more complex in structure. The following classification may help to indicate the common character of these substances:—

THE LIPIDES.—All the ether soluble derivatives of fatty acids included in one of the following classes:—

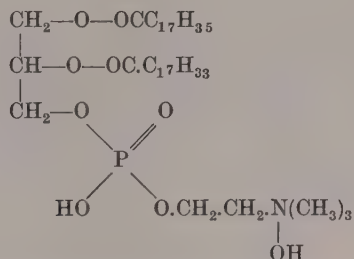
(1) *Neutral Fats*.—Neutral esters of glycerol and fatty acids.

(2) *Waxes*.—Neutral esters of higher monohydric alcohols (cetyl alcohol, cholesterol, &c.) and fatty acids.

(3) *Phospholipides or Phosphatides*.—Compounds of an alcohol (glycerol), fatty acids, phosphoric acid and an organic base.

(4) *Glycolipides or Galactosides (Cerebrosides)*.—Compounds of a carbohydrate (galactose), fatty acids and an organic base.

The chief phospholipide is lecithin. The organic base present in its molecule is choline. The nature of the fatty acids is uncertain and, in all probability, it varies with the tissue from which the lecithin has been derived. In general, the fatty acids are more highly unsaturated than those of the food or the reserve fats of the animal—a fact which suggests that the desaturation of fatty acids is an important preliminary to their metabolism. There are various lecithins, one of which is probably represented by the following formula in which the two fatty acids are represented by stearic acid and oleic acid:—



Other acids, *e.g.* palmitic, linoleic or linolenic, may be present instead of the two shown.

Lecithin is a very unstable substance to oxygen owing to the highly unsaturated acids present, and for this reason extreme precautions must be taken in its preparation from tissues if it is desired to avoid contamination with complex oxidation products. Much of the work on the physiological effect of the phospholipides is probably vitiated by the presence of these impurities. On the other hand, the universal distribution of lecithin signifies an important function in cellular activity. It undoubtedly plays an important part in the transport and metabolism of fats related, on the one hand, to the fact that it is capable of colloidal solution in water facilitating its free transport, and on the other, to the desaturation which is associated with its production from neutral fats. It is not improbable also that the

phosphoric acid of the phospholipides is concerned in the synthesis of the phosphorus-containing nucleoproteins of the cell, and perhaps also in the normal processes of carbohydrate metabolism. Apart altogether from the chemical significance of its constituents, it is certain that lecithin and the allied substances, by virtue of their special physico-chemical condition in solution, play an important part in determining the peculiar permeabilities, osmotic relations and surface conditions of the cell.

The glycolipides are found chiefly in nervous tissue, and are generally prepared from the acetone extract of brain. They contain no phosphoric acid, and the organic base present is a complex substance called sphingosine. They are relatively more stable to oxygen than is lecithin.

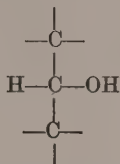
The characterisation of individual lipides is a matter of much difficulty owing to their instability, to the similarity of their general properties, and to their eccentric solubilities. The following are the only ones definitely established as individuals :

- Phospholipides : Lecithin, contains the base choline.
 Cephalin, contains the base amino-ethyl alcohol,
 $\text{CH}_2\text{OH}.\text{CH}_2\text{NH}_2$.
 Sphingomyelin.
- Glycolipides : Phrenosin.
 Kerasin.

2. THE CARBOHYDRATES

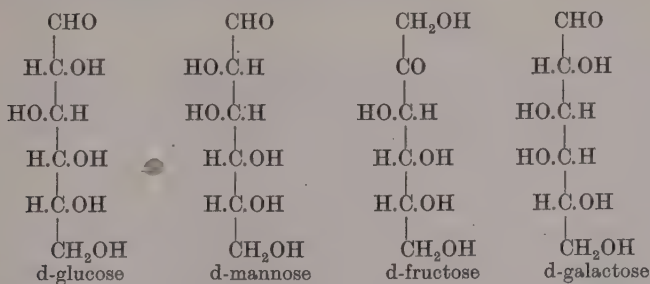
The Carbohydrates are a group of bodies of wide distribution and great importance in both the vegetable and animal kingdoms. In plants the first product of assimilation of carbon is a carbohydrate, and in animals these substances form one of the most important sources of energy. They consist of the elements carbon, hydrogen and oxygen, the two last-named being almost invariably in the proportions necessary to form water. It is on this account that the term carbohydrate has been given to the group. Their general formula might be expressed $\text{C}_n\text{H}_{2n}\text{O}_n$. Certain derivatives of the group, obtained by the substitution of methyl and other radicals for a hydrogen atom, though necessarily classified with carbohydrates on account of their reactions, do not conform to this general formula, *e.g.* rhamnose, $\text{C}_6\text{H}_{12}\text{O}_5$. All the carbohydrates which are of importance in the animal economy contain six carbon atoms or a multiple of this number. Analogous substances however can be prepared containing less or more than this number of carbon atoms. A series of compounds exist which contain in their molecule 2, 3, 4, 5, 6, 7, 8, 9 carbon atoms, and are termed dioses, trioses, tetroses, pentoses, hexoses, heptoses, and so on ; the termination 'ose' with the Greek numeral prefixed, indicating the number of carbon atoms, gives them a distinct designation. These are all oxidation products of polyatomic alcohols, being either ketones or aldehydes of these alcohols and known as ketoses and aldoses respectively. Thus from glycerol we may obtain glyceryl aldehyde $\text{COH}.\text{CHOH}.\text{CH}_2\text{OH}$ and dioxycetone $\text{CH}_2\text{OH}.\text{CO}.\text{CH}_2\text{OH}$. Both these substances behave as sugars and belong to the group of trioses. They are generally obtained together and are called glycerose. From the hexatomic alcohol $\text{CH}_2\text{OH}.\text{(CHOH)}_4.\text{CH}_2\text{OH}$ we may obtain either the aldehyde $\text{COH}.\text{(CHOH)}_4.\text{CH}_2\text{OH}$ or the ketone $\text{CH}_2\text{OH}.\text{CO}.\text{(CHOH)}_3.\text{CH}_2\text{OH}$. All these compounds are distinguished by the termination 'ose.' It is convenient to call those compounds containing six carbon atoms the sugars, because it is to this group that the natural sugars belong.

Stereoisomerism in the Sugars. It will be noticed that of the six carbon atoms contained in the hexose molecule, *e.g.* the aldose $\text{COH}(\text{CHOH})_4\text{CH}_2\text{OH}$, four are *asymmetric*, *i.e.* their four combining affinities are saturated with groups of different kinds, *viz.* two carbon atoms, one H atom, and one OH group



They must therefore present many stereoisomeric forms. If n represent the number of asymmetric carbon atoms in a compound, the possible number of stereoisomers is 2^n . Thus an aldehydohexose with four asymmetric carbon atoms $(\text{CHOH})_4$ must present 2^4 isomers, *i.e.* sixteen isomeric compounds, so that there must be sixteen sugars all possessing the formula $\text{CH}_2\text{OH}(\text{CHOH})_4\text{COH}$, in addition to the inactive sugars obtained by a mixture of two oppositely active members of this group. Of the sixteen possible sugars of this formula, as many as fourteen have been found or have been artificially prepared. Only a small number are however of any physiological importance. These include the aldoses, glucose, mannose and galactose, and the ketose, fructose or lævulose. All the other sugars are unassimilable by the animal cell and are not manufactured by plants.

Since these sugars can be divided into the optically active and the inactive varieties, an obvious mode of designation would be to represent them as d-, l-, and i- varieties respectively, *i.e.* dextro-rotatory, lævo-rotatory, and inactive. On Fischer's suggestion however, this mode of nomenclature has been altered in favour of representing by the letter prefixed, not the optical qualities of the substance in question, but its relation to other substances, especially glucose. Thus, d-fructose means that fructose is the ketose corresponding to the dextro-rotatory glucose, d-fructose itself being lævo-rotatory, though its active asymmetric C atoms are identically arranged with those in glucose. With this limitation one may say that it is only the d-hexoses of a particular form which are assimilable, and therefore of physiological importance. The small differences in the configuration of the four d-sugars can be readily seen if their graphic formulæ be compared :



THE PENTOSES. ($\text{C}_5\text{H}_{10}\text{O}_5$)

These bodies occur largely in plants in the form of complex polysaccharides, the Pentosans, which give Pentoses on hydrolysis with acids. Two forms of pentose have been found in the animal body, namely, i-arabinose, which has been isolated from the urine in cases of pentosuria, and l-xylose (or d-ribose, Levene), which occurs built up into the nucleic acid molecule of the pancreas and other organs. The pentoses can

apparently be utilised by herbivora as foodstuffs. We know nothing as to the part they play in the animal body or as to the causation of the rare condition of pentosuria.

THE HEXOSES

Only four Hexoses out of the large number which have been synthesised are assimilable by the animal body. These are mannose, glucose, galactose and fructose, the three former being aldoses, while the last is a ketose. All of them are derivatives of d-glucose. They may be synthesised in several ways. The most interesting, because it probably represents the mechanism of synthesis of hexoses in plants, is the formation from formaldehyde. In alkaline solutions formaldehyde polymerises with the formation of a mixture of hexoses known as acrose. From this mixture α -acrose can be isolated by the formation of its osazone and the reconversion of this osazone into sugar. It is found to be identical with i-fructose.

GLUCOSE, DEXTROSE or GRAPE SUGAR is the chief constituent of the sugar of fruits, especially of grapes. It occurs in the body as the end product of the digestion of starch. When pure it forms white crystals which melt at 100°C . and lose the one molecule of water of crystallisation at 110°C . It is easily soluble in water, and the solution shows mutarotation. Its final specific rotatory power at 20°C . is $[\alpha]_D = + 52.74^{\circ}$.

d-FRUCTOSE or LÆVULOSE occurs mixed with glucose in honey and in fruit sugar. It is also, with glucose, formed by the digestion or inversion of cane sugar. It is crystallisable with difficulty. Its watery solution is lævo-rotatory, and reduces Fehling's solution somewhat less strongly than glucose, its reducing power being 92, if we take that of glucose as 100. It ferments readily with yeast; with phenyl hydrazine it gives the same osazone as is formed from glucose.

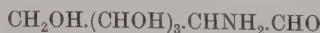
GALACTOSE is formed by the digestion or hydrolysis of milk sugar or lactose. It is also obtained on hydrolysing the galactosides of the brain with dilute mineral acids, and by the hydrolysis of certain vegetable gums. It is much less soluble in water than glucose. It is dextro-rotatory and shows marked mutarotation. With ordinary yeast it ferments, but extremely slowly. One species of yeast is known, namely *saccharomyces apiculatus* which, while fermenting d-fructose and glucose, has no effect on galactose. This yeast can therefore be used to isolate galactose from a mixture of the monosaccharides. It reduces Fehling's solution, its reducing power being somewhat less than that of glucose. Yeasts can be trained to ferment galactose.

MANNOSE. Mannose, though an assimilable sugar, is of such rare occurrence in our foodstuffs that it plays practically no part in animal physiology. It is dextro-rotatory, reduces Fehling's solution, ferments easily with ordinary yeast, and gives an osazone which is identical with that derived from glucose.

DERIVATIVES OF THE HEXOSES

Two derivatives of glucose are of considerable physiological importance, namely, glucosamine and glycuronic acid.

GLUCOSAMINE, $\text{C}_6\text{H}_{13}\text{NO}_5$, has the structural formula :



It is obtained from chitin, which forms the exoskeleton of large numbers of the invertebrata, by boiling this with concentrated hydrochloric acid. It is obtained as a decomposition product of the glucoproteins, such as the mucins. In solution it is dextro-rotatory, reduces Fehling's solution, and gives an osazone resembling that derived from glucose.

GLYCURONIC ACID, $C_6H_{10}O_7$, may be regarded as one of the first results of oxidation of the glucose molecule. The group which has undergone oxidation is not the readily oxidisable CHO group, but the CH_2OH group at the other end of the molecule. The formula of this acid is therefore :



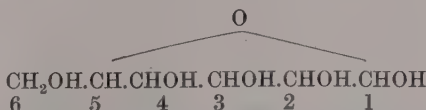
It may be produced by the oxidation of glucose by means of hydrogen peroxide. In the free state it does not occur in the animal body. It is constantly found in the urine after administration of certain drugs such as phenol, camphor or chloral, and then occurs as a conjugated acid with these substances. These conjugated acids are lævo-rotatory, though the free acid is dextro-rotatory. In the free state it reduces Fehling's solution and gives an osazone which is not sufficiently characteristic to distinguish from glucosazone. It does not undergo fermentation with yeast. This test is therefore the best means of distinguishing the acid in urine from glucose.

THE FORMATION OF GLUCOSIDES

The formulæ already given for the hexoses suffice to explain the majority of the reactions of the sugars and are in general use; but a study of the behaviour of the reducing sugars in solution indicates that they possess a structure more labile than is suggested by the conventional static formula. A sample of glucose which has been recrystallised from water, when dissolved in water exhibits a progressive decrease in rotatory power over a period of about twenty-four hours, during which the specific rotation falls from about 100° to a constant value of 52.5° . On the other hand a specimen of glucose recrystallised from pyridine gives, upon solution in water, an initial specific rotation of about 20° , rising in the same period to 52.5° . This phenomenon receives the name of mutarotation, and is understood to indicate that in solution glucose exists as an equilibrium mixture of two optical isomers which are designated α and β glucose respectively. α Glucose is less soluble in water than the β form, and so is the isomer usually handled as solid glucose. On the other hand, β glucose is obtained when the sugar is crystallised from water above $98^\circ C.$, or from pyridine.

These considerations receive confirmation from the preparation of two monomethyl derivatives of glucose by treatment of a methyl alcoholic solution of the sugar with dry hydrochloric acid gas. These derivatives—the methyl glucosides—are the methyl ethers of the two forms of glucose, which have been stabilised by the introduction of the methyl group. Upon hydrolysis they yield glucose which exhibits a downward and an upward mutarotation respectively.

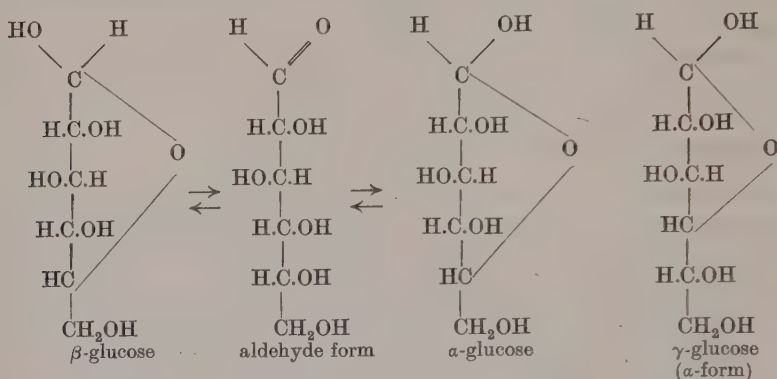
The structural form of these isomers was a matter of surmise until the work of Irvine and his associates developed a method of methylation of the sugars whereby all the hydroxy groups may be converted into methyl ethers. An examination of the methylated sugars thus produced renders it possible to decide to which of the carbon atoms of the sugar the hydroxyl groups are attached. In the case of glucose a pentamethyl glucose is obtained in which the methyl groups appear to be attached to the carbon atoms 1, 2, 3, 4, 6 (numbering from the aldehyde carbon). This means that every carbon atom of glucose except the fifth carries a hydroxyl group, and can only be explained by the existence in the molecule of a lactone ring.



It will be observed that by this modification an asymmetric carbon atom has been created in position 1, accounting at once for the two labile forms of

the sugar. In its simplest expression mutarotation is a type of keto-enolic change involving the shift of a labile hydrogen atom.

Recent work has also shown in other ways that in solution under ordinary conditions the oxygen is linked as a 1 : 5 (amylenic oxide) linkage on to the carbon chain, giving α and β glucose; a 1 : 4 or γ lactone linkage can also exist, being a very reactive form called γ glucose, of which again there are α and β forms.



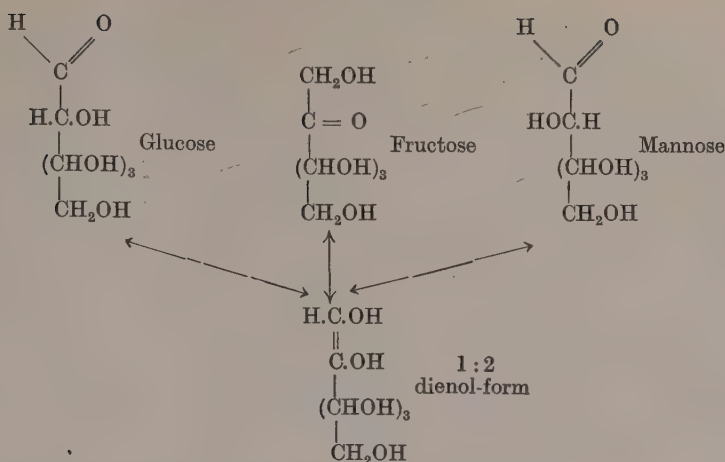
A solution of a hexose must therefore be regarded as an equilibrium mixture of the α and the β forms and the aldehydic structure. The addition of a trace of alkali to a fresh solution of glucose immensely accelerates the rate of mutarotation, indicating an increased lability of the sugar molecule in alkaline solution.

A large number of glucosides occur as plant products—amygdalin, salicin, phloridzin, indican, saponin—and appear to be β glucosides, *i.e.* are ethers formed from β glucose and an alcohol. The disaccharides are also glucosides: thus maltose is glucose α glucoside, whilst lactose is probably glucose β galactoside.

THE ACTION OF ALKALI ON THE HEXOSES

We have seen that a trace of alkali greatly accelerates the mutarotation of the hexoses, indicating an increased lability of the terminal carbon atom. In more strongly alkaline solutions pronounced changes occur. In the case of glucose a progressive fall in rotatory power reaching a lævo-rotation will be observed. Examination of the solution will then show the presence not only of glucose but also of fructose and mannose. Reference to the structural formulæ of these sugars will remind the reader that the differences between these three hexoses are confined to the two terminal carbon atoms, and it will be seen that their ready interconversion in alkaline solution may be explained as occurring through the intermediate production of an 'enol-form.'

It is of interest that these three hexoses, which are most nearly related *in vitro*, are also the most readily assimilated by the animal. The difference is that, whereas alkali effects an indiscriminate interconversion of glucose, fructose and mannose, the living cell shows directional activity in turning them all into glucose. The anomalous position of galactose as an assimilable sugar is not capable of so facile an explanation on structural lines. It is however less readily assimilated than the other three hexoses and occupies a rather peculiar position in mammalian physiology.



In strongly alkaline solutions of the hexoses still more extensive changes occur. A large number of different hexoses, trioses and dioses appear, together with acids containing varying numbers of carbon atoms, such as oxalic, lactic, tartaric and saccharic acids, and complex resinous substances. This evidently indicates an instability of the carbohydrate chain throughout its entire length even to the extent of fragmentation into carbon chains of varying lengths. The reaction of a hexose to alkali has been likened to the irritability of the earthworm—there is a diminution in sensitivity towards the tail end. There is so much in common between the alkaline and the biochemical degradation of carbohydrate that one is persuaded that the same broad lines are followed in each, though in the living cell the notable distinction is the specific direction of the change towards the production of a selected few of the substances appearing in alkaline solution *in vitro*.

THE DISACCHARIDES

The disaccharides are formed by the union of two molecules of monosaccharides with the elimination of one molecule of water, and can be regarded, according to the manner in which the molecules are combined, as glucosides, galactosides, &c. On hydrolysis, *e.g.* on heating with acids, they take up one molecule of water and are split up into the corresponding monosaccharides. Thus cane sugar gives equal parts of glucose and fructose, maltose gives two molecules of glucose, while milk sugar or lactose gives equal parts of glucose and galactose.

CANE SUGAR, sometimes known as saccharose, is widely distributed throughout the vegetable kingdom, and forms an important article of diet. It has no reducing power on Fehling's solution. It is strongly dextro-rotatory and has a specific rotatory power of $+66.5^\circ$. On hydrolysis it is converted into equal molecules of glucose and fructose. Owing to the fact that fructose rotates polarised light more strongly to the left than glucose does to the right, the mixture of the two monosaccharides so obtained is lævo-rotatory. On this account the change from free cane sugar to the mixture of monosaccharides is known as *inversion*, and the mixture is often spoken of as 'invert sugar.' The term inversion has since been loosely applied to the process of hydrolysis itself, so that we often speak of the inversion of maltose or of lactose, meaning thereby the hydrolysis of these sugars with the production of their constituent monosaccharides. With yeast, cane sugar first undergoes inversion by a special enzyme present in the yeast (*invertase*), and the mixture of fructose and glucose is then fermented.

MALTOSE is formed during the hydrolysis of starch by acids or by digestive enzymes, and is also the chief sugar in germinating barley or malt. It is strongly dextro-rotatory, ferments easily with yeast, and reduces Fehling's solution; its reducing power is about 70 per cent. of that of glucose. With phenyl hydrazine it gives phenyl maltosazone, which forms characteristic yellow crystals with a melting-point of 206°C .

MILK SUGAR or LACTOSE is found only as a constituent of milk. It forms colourless rod-like crystals, which are much less soluble in water than are the two other disaccharides. It is much less sweet than either cane sugar or maltose. It is dextrorotatory and shows mutarotation. It is not fermented by ordinary yeast. Before fermentation can occur the lactose must be split by the agency of acids or by an enzyme, lactase, which occurs in the animal body and in certain moulds, into the monosaccharides glucose and galactose. Lactose reduces Fehling's solution and gives with phenyl hydrazine lactosazone, which is easily soluble in hot water and therefore does not come down until the fluid is cold.

THE POLYSACCHARIDES ($\text{C}_6\text{H}_{10}\text{O}_5$) $_n$

In the animal body, where the supporting tissues are composed chiefly of derivatives of proteins, the sole significance of polysaccharides lies in their value as foodstuffs. In plants, anhydrides both of hexoses and pentoses occur in bewildering variety. Unlike the other carbohydrates, the higher polysaccharides are not destroyed by hot strong alkaline solutions. The chemical constitution of the polysaccharides is a difficult problem to approach because of their complexity and their colloidal behaviour. The methylation methods of Irvine, to which reference has already been made, have given us a deeper insight into the manner of combination of the hexoses in a polysaccharide molecule, though progress is as yet insufficient for confident conclusions to be drawn.

STARCH is present in large quantities in nearly all vegetable foods, and is an important constituent of the cereals, from which flour and bread are derived, as well as of tubers, such as the potato. In the plant cells it occurs as concentrically striated grains. It is insoluble in cold water. In hot water the grains swell up and burst, forming a thick paste, which sets to a jelly on cooling. This semi-solution, as well as the original starch grains, gives an intense blue colour on the addition of iodine. On treating starch with cold alkalis or cold dilute acid, it is converted into a soluble modification, the so-called soluble starch or *amylodextrin*, which also gives a blue colour with iodine. This modification is likewise produced as the first stage of the action of diastatic enzymes upon starch. On boiling with dilute acids, starch is converted first into a mixture of dextrins, then into maltose, and finally into glucose. On acting upon starch with various enzymes, such as the diastase which may be extracted from malt or germinating barley, or with the amylase occurring in saliva or pancreatic juice, it undergoes hydrolysis, the final result of the action being a mixture of four parts of maltose to one part of stable dextrin. As to the intermediate stages in this reaction opinions are still divided. The first product is soluble starch or *amylodextrin*. This breaks up into a reducing sugar and another dextrin, *erythro-dextrin*, which gives a red colour with iodine; and this dextrin, on further hydrolysis, yields reducing sugar and *achroo-dextrin*, which is not coloured by the addition of iodine. Thus there is a series of successive hydrolytic decompositions of the molecule, each resulting in the splitting off of a molecule of sugar and the production of a lower dextrin. The starch grain is believed to consist of two substances, *amylose* and *amylopectin*, in the

ratio 2 : 1. The latter is closely associated with phosphoric acid, with which it may indeed be in combination. On acid hydrolysis both yield glucose; on hydrolysis with barley diastase amylose yields maltose, but amylopectin is only partially depolymerised, though oat diastase can split it also finally into maltose.

There is some evidence that both amylose and amylopectin are formed by polymerisation of units which consist of anhydrides of hexasaccharides. The relation between the two constituents of the starch grain and soluble starch is not clear, and estimates of the number of glucose molecules in starch range from 7 to 200,—evidence of the difficulties attending the investigation of substances which exist in solution in the colloidal state.

The DEXTRINS are ill-defined bodies which are difficult to separate. They are amorphous white powders, easily soluble in water, forming solutions which, when concentrated, are thick and adhesive. They are insoluble in alcohol and ether. With cupric hydrate and caustic alkali they form blue solutions, which reduce slightly on boiling. They are not precipitated by saturation with ammonium sulphate. On boiling with dilute acids, they are converted entirely into glucose.

INULIN, which somewhat resembles starch, occurs in dahlia tubers. It is easily hydrolysed by weak acids into d-fructose or lævulose.

GLYCOGEN is a polysaccharide which closely resembles starch in structure and properties. It is found in the liver, muscles and other tissues of the body, in all foetal tissues, and in yeast. It is a white powder, soluble in water, forming an opalescent solution. It is precipitated from its solution on the addition of alcohol to 60 per cent., or by saturation with solid ammonium sulphate. On boiling with acids, it is entirely converted into glucose. It is affected by the enzymes diastase and amylase, in the same way as vegetable starch, giving first dextrins and finally a mixture of maltose and dextrin. With iodine it gives a mahogany-red colour which, like the blue colour produced in starch, is destroyed by boiling, to return again on cooling. We shall have occasion to consider its properties more fully when we are dealing with the functions of the liver.

THE CELLULOSES. Cellulose is a colourless, insoluble material, or mixture of materials, which forms the cell walls of the younger parts of plants, and is therefore a constituent of most of our vegetable foods. It is insoluble in water or dilute acids or alkalies, but soluble in ammoniacal cupric oxide solution. On boiling with strong acids, it gradually undergoes hydrolysis and yields glucose. In herbivorous animals cellulose undergoes digestive changes and forms an important constituent of their food. The solution of the cellulose in this case is carried out by the agency, not of enzymes secreted by the wall of the gut, but of micro-organisms which swarm in the paunch of ruminants and in the cæcum of other herbivora. In some cases the effective agent is a cytase present in the vegetable cells themselves. Since this enzyme is destroyed by boiling, cooked hay is much less digestible than hay in the raw condition. In certain invertebrata it seems probable that a true cellulose-digesting enzyme, or cytase, is secreted by the walls of the alimentary canal. In man cellulose undergoes practically no change in digestion, and serves merely by its bulk to promote peristalsis and the normal evacuation of the bowels.

3. THE PROTEINS

The Proteins form the most important constituent of living protoplasm. On this account protein must always be present in the food to supply the

material necessary for building up new protoplasm in the growing animal and for replacing the waste of living material which is taking place in the discharge of its normal functions. Regarding the complexity of reaction presented by living protoplasm as determined in the first instance by the chemical and physical complexity of this material itself, we should expect to find that the proteins forming its main constituents would themselves partake of some of this quality. The carbohydrates and fats, although in many cases made up of huge molecules, are nevertheless built up on a very simple type. Their molecular weight is very large, but their molecules are simple in structure. When however we break up a protein molecule, we meet with a great number of subsidiary groups, the presence of which is essential to the making of a nutritive protein.

Owing to this complexity of structure it is not easy to give a simple definition in chemical terms of what we mean by the term 'protein.' It is necessary rather to describe certain of the qualities presented by this group, the possession of which is regarded as essential to the conception of a protein.

Elementary Composition. All proteins contain oxygen, hydrogen, nitrogen, carbon and usually sulphur. The proportion of these elements in the various proteins may be represented as follows :

C	50.6-54.5	per cent.
H	6.5- 7.3	" "
N	15.0-17.6	" "
S	0.3- 2.2	" "
O	21.5-23.5	" "

Nearly all contain a small trace of phosphorus varying from 0.4 to 0.8 per cent., but it is doubtful how far this forms an integral part of the protein molecule.

Physical Characters. The proteins are amorphous indiffusible substances belonging to the class of bodies known as colloids. Most of them are soluble either in water, weak salt solutions, or in dilute acids or alkalies. They are inert bodies and tasteless. As is the case with most colloids when in solution or pseudo-solution, they can be brought into an insoluble form by various simple agencies, such as shaking, change of temperature, alteration of reaction, or addition of neutral salts. Coagulation by heat forms a distinguishing feature of a number of members of this class, which are therefore spoken of as 'coagulable proteins.' For instance, white of egg is a solution of different proteins. On diluting it with weak salt solution no precipitation takes place. If however the solution be heated to about 80° C. a precipitate of coagulated protein is formed. If a strong solution be boiled the whole fluid sets to a solid white mass (hydrogel). This change is irreversible, *i.e.* it is not possible by lowering the temperature to bring the white of egg again into solution, and many properties of the protein have been changed in the act of coagulation. With certain proteins and their allies the coagulation on change of temperature is a reversible process. Thus an alkaline solution of caseinogen, the chief protein of milk, if treated with a little calcium chloride and heated, undergoes coagulation and sets into a jelly, but on cooling the mixture the coagulum once more enters into solution. Ordinary gelatin with water forms a solid jelly below 20° C., and a fluid solution above this temperature.

The Molecular Weight of Proteins. We may arrive at an approximate idea of the minimum size of the protein molecule in various ways, though in all cases our calculations are apt to be vitiated by the difficulty of obtaining a preparation which is homogeneous, *i.e.* chemically pure, and by the ease with which molecules of the size which we must assume for proteins form

adsorption combinations in varying proportions with other substances. Some idea of the molecular complexity represented by these weights may be gained by writing out the possible empirical formulæ of the various proteins, *e.g.* :

Egg albumin	$C_{204}H_{322}N_{52}O_{66}S_2$
Protein in hæmoglobin (from horse)	$C_{680}H_{1098}N_{210}O_{241}S_2$
Protein in hæmoglobin (from dog)	$C_{725}H_{1171}N_{194}O_{214}S_2$
Crystallised globulin (from pumpkin seeds)	$C_{292}H_{481}N_{20}O_{83}S_2$

If we assume that each molecule of the respective protein contains only one atom of sulphur, we can calculate its empirical molecular weight. It is evident that the protein which contains 1 per cent. of sulphur will have a molecular weight of not less than 3200.

The greater part at any rate of the sulphur in the protein molecule occurs as a constituent of a substance, cystine, each molecule of which contains two atoms of sulphur, and we must regard double the empirical molecular weight as the minimum molecular weights of these various proteins. We should thus obtain figures like the following (Abderhalden) :

	Sulphur per cent.	Empirical Molecular weight.	Minimal probable Molecular weight.
Edestin	0.87	3680	7360
Oxyhæmoglobin (horse)	0.43	7440	14880
Serum albumin (horse)	1.89	1700	3400
Egg albumin	1.30	2460	4920
Globulin	1.38	2320	4640

With some proteins we may make use of other elements to arrive at an idea of the approximate molecular weight. Thus oxyhæmoglobin contains between 0.4 and 0.5 per cent. iron. If we assume that each molecule of oxyhæmoglobin contains one atom of iron, its molecular weight must be about 16,000.

Some clue to the size of the protein molecule is afforded by determinations of the osmotic pressure or molecular concentration of their solutions by physical methods. When we determine the freezing-point or boiling-point of protein solutions, the depression of freezing-point, or elevation of boiling-point is so small that it falls within the limit of experimental error or is no greater than can be accounted for by the inorganic salts present in the solution. Since however colloidal membranes, such as films of gelatin or vegetable parchment, are impervious to proteins, we can directly determine the osmotic pressure of their solutions. The colloidal constituents of egg albumin or serum solutions are found to give an osmotic pressure such that 1 per cent. protein corresponds to about 4 mm. Hg pressure. This would indicate a molecular weight for the serum proteins of about 30,000. A determination of the osmotic pressure of hæmoglobin by Adair gave a molecular weight about 67,000. These results however must be received with caution, since we are not necessarily justified in applying to these gigantic molecules data derived from a study of smaller molecules such as salt or sugar. Even if we accept these determinations of osmotic pressure as indicating the molecular weights just quoted, it is evident that a very slight degree of aggregation of the molecules into larger complexes will bring the osmotic pressure below the point at which it is measurable, and would transform the solution into a suspension of particles in which one could not expect to find any osmotic pressure whatsoever. On the other hand, the osmotic pressure

of the protein will also be influenced by the ionisation of the protein should it under the conditions of the experiment be present as a salt.

THE STRUCTURE OF THE PROTEIN MOLECULE

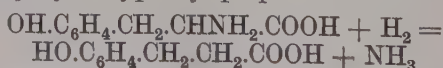
We can arrive at some idea of the manner in which the protein molecule is built up only by breaking it down bit by bit, employing methods which, while resolving the large molecule into its proximate constituents, will not act too forcibly in changing the whole arrangements of these constituents. The relation of the starches or polysaccharides to the sugars was found by studying the hydrolysis of the former, and it is by the hydrolysis of the proteins that we have arrived at most of our present knowledge of their constitution. Contributory evidence may also be gained by the use of oxidising agents or by employing the refined methods of analysis possessed by certain living organisms—bacteria, by which means we can often effect limited oxidations or reductions or can replace an NH_2 group by H, or a COOH group by H.

Acid Hydrolysis of Proteins. For this purpose rather stronger acids are used than for the hydrolysis of starch. The protein is heated for twenty-four hours either with concentrated hydrochloric acid together with a certain amount of stannous chloride to prevent any oxidation taking place, or with 25 per cent. sulphuric acid. We obtain in this way an acid fluid containing an extremely complex mixture of various substances, all of which belong to the class of amino-acids, and must be regarded as the proximate constituents of the protein molecule.

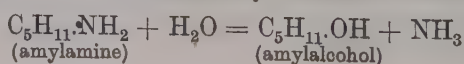
A similar hydrolytic change may be effected by the use of digestive enzymes obtained either from the alimentary canal of higher vertebrates or from certain plants. Thus we may use pepsin, the active constituent of the gastric juice, trypsin, the proteolytic enzyme secreted by the pancreas, papain or other vegetable enzymes obtained from papaya, from pineapple juice, and so on. These enzymes are all milder in their action than the strong acids. Pepsin for instance effects only a partial decomposition of the protein molecule. Its action results in the formation of substances which still present all the protein reactions and are classified as hydrated proteins or as proteoses and peptones. Trypsin carries the protein a stage further and gives a mixture of amino-acids. Certain groups however of the protein molecule present a considerable resistance to the action of trypsin, so that when its action is complete these groups are still found not yet broken down into their constituent amino-acids.

The putrefactive processes determined by the action of bacteria in solutions of proteins are somewhat too complicated in their results to throw much illumination on the structure of the protein molecule itself. This method is however of extreme value when it is applied to isolated constituents of the proteins. Under the action of these bacteria we may have a process of deamination which may be accompanied by simple hydrolysis or by reduction. In the former case an amino-acid may be converted into an hydroxyacid, in the latter case into a fatty acid.

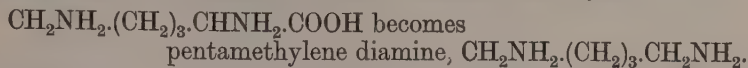
Thus tyrosine under the action of bacteria of putrefaction may split up into ammonia and *p*-hydroxyphenyl propionic acid :—



Under the action of yeasts an amine may become an alcohol :—



On the other hand, some bacteria may split off carbon dioxide from the amino-acids and yield amines. Thus the diamino-acid, lysine,

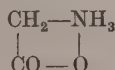


Tyrosine becomes *p*-hydroxyphenylethylamine, a substance having marked physiological effects. Phenylalanine $\text{C}_6\text{H}_5.\text{CH}_2.\text{CH}.\text{NH}_2.\text{COOH}$, becomes phenylethylamine $\text{C}_6\text{H}_5.\text{CH}_2.\text{CH}_2.\text{NH}_2$. These reactions are therefore of value in determining the exact grouping of the atoms in the more complex of the proximate constituents of the proteins.

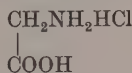
Since all the known disintegration products of the main protein molecule are amino-acids, it may be of value to point out some of the distinguishing features of this class of bodies.

Properties of Amino-Acids. All the amino-acids, except glycine, derived from proteins are optically active, whereas those obtained by synthesis are inactive, and special means have to be devised in order to obtain from the artificially formed racemic amino-acid either the *d*- or *l*-amino-acid.

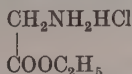
The presence in the amino-acids of the basic radical NH_2 and of the acid group COOH lends to these bodies a double character. In themselves, possessing neither acid nor alkaline reaction, they are able in the presence of strong acids or bases to act either as base or acid. When in solution by themselves it is possible that there is an actual closing of the ring by a soluble union between the NH_2 group and the COOH group, so that *e.g.* the formula of glycine may be :



When such a neutral compound is treated with acid this bond is loosed and we have the salt of the amino-acid. Thus, with hydrochloric acid, glycine forms glycine hydrochloride :



a salt which still possesses an acid group and which is therefore capable of combining with ethyl to form the hydrochloride of the ester of the amino-acid. Thus :



With bases the amino-acids form salt-like compounds such as potassium amino-acetate :



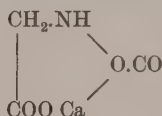
Amino-acids also combine as acids and bases with one another. This power of combination much increases the difficulty of separating the constituents from a mixture of amino-acids. Amino-acids, which singly are extremely insoluble, are often soluble when in the presence of other amino-acids.

On account of the dual nature of the amino-acid molecule, these substances act as feeble conductors of the electric current, *i.e.* as electrolytes. The charge carried by an amino-acid and its ionisation depends upon the conditions in which it is placed. Since it may act either as the cation or the anion, it is spoken of as an *amphoteric* electrolyte.

Since proteins are polypeptides built up from a large number of amino-acids, it is not surprising to find that they likewise are amphoteric substances. The predominance of acid or basic properties will depend on whether the protein contains a surplus of dicarboxylic acids or of di-amino acids. It follows that the proteins can exist either as salts with acids or with bases or in the free state. The factor which determines the condition of the protein is the hydrogen ion concentration. It has been found that the physical properties of protein solutions vary greatly with the hydrogen ion concentration and exhibit abrupt maxima or minima at a definite reaction which is characteristic

of the protein. It seems probable that at this point—the iso-electric point—the protein is combined neither with acids nor with bases, but exists as a very feebly ionised free protein. On either side of the iso-electric point a highly ionised protein salt of some sort will exist, the nature of which again depends on the hydrogen ion concentration. These characteristic changes of the protein molecule with the reaction of the medium promise to be very helpful in the interpretation of many difficult phenomena in connection with the physical chemistry of the cell—permeability, osmosis, imbibition, adsorption and the action of proteolytic enzymes.

One reaction of the amino-acids of interest is the formation of carbamino-acids. If a stream of carbon dioxide be passed into a mixture of an amino-acid, *e.g.* glycine, with lime, the carbon dioxide is taken up. On filtering the mixture a clear liquid passes through, which gradually in course of time deposits a precipitate of calcium carbonate. The filtrate first obtained contains a compound of calcium, calcium glycine carbonate. The formula is as follows :

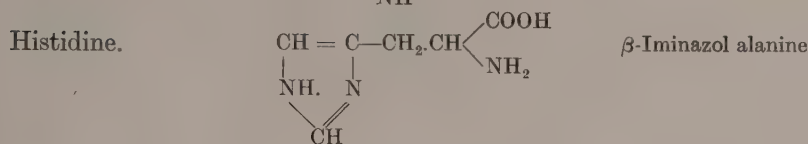
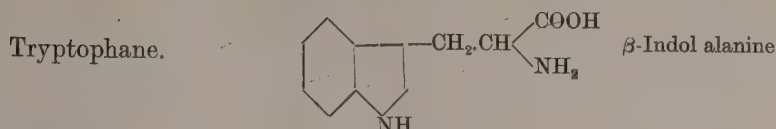
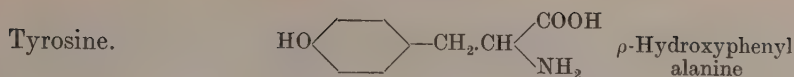


THE DISINTEGRATION PRODUCTS OF THE PROTEINS

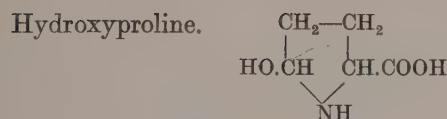
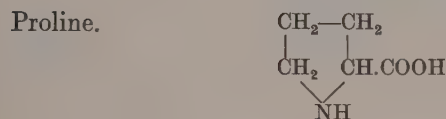
The amino-acids which have been isolated from the products of hydrolysis of proteins are so varied that it may be a convenience to append a list of the physiologically important amino acids. Most of these have actually been separated by hydrolysis of proteins.

Monamino monocarboxylic Acids

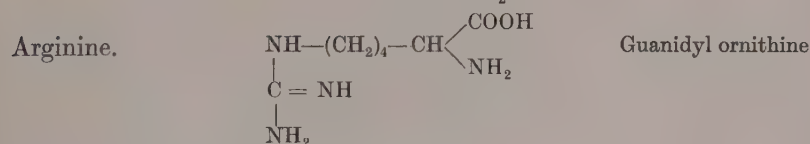
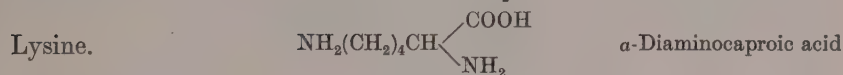
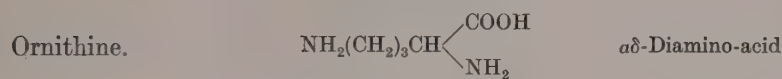
Glycine.	$\text{NH}_2\text{CH}_2\text{COOH}$	α -Amino acetic acid
Alanine.	$\begin{array}{c} \text{COOH} \\ \diagup \\ \text{CH}_3\text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	α -Amino propionic acid
Serine.	$\begin{array}{c} \text{COOH} \\ \diagup \\ \text{HOCH}_2\text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	β -Hydroxy-alanine
Valine.	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{CH}_3 \end{array} \text{CH} \begin{array}{c} \text{COOH} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	$\beta\beta$ -Dimethyl alanine
Leucine.	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{CH}_3 \end{array} \text{CH} \text{CH}_2 \text{CH} \begin{array}{c} \text{COOH} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	β -Isopropyl alanine
Isoleucine.	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array} \text{CH} \text{CH} \begin{array}{c} \text{COOH} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	$\beta\beta$ -Methyl ethyl alanine
Cystine.	$\begin{array}{c} \text{COOH} \\ \diagup \\ \text{HS.CH}_2\text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	β -Thio-alanine
Cystine.	$\begin{array}{c} \text{COOH} \\ \diagup \\ \text{S.CH}_2\text{CH} \\ \diagdown \\ \text{NH}_2 \\ \\ \text{S.CH}_2\text{CH} \\ \diagdown \\ \text{NH}_2 \\ \\ \text{COOH} \end{array}$	Dicystine
Methionine.	$\text{CH}_3\text{S}(\text{CH}_2)_2\text{CH}(\text{NH}_2)\text{COOH}$	γ -Methylthiol — α -Amino butyric acid
Phenyl alanine.	$\text{C}_6\text{H}_5\text{CH}_2\text{CH} \begin{array}{c} \text{COOH} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{NH}_2 \end{array}$	Phenyl alanine



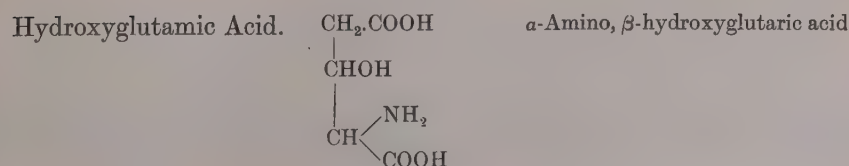
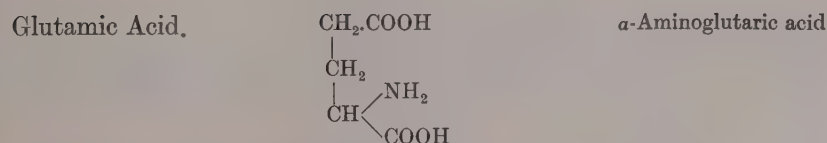
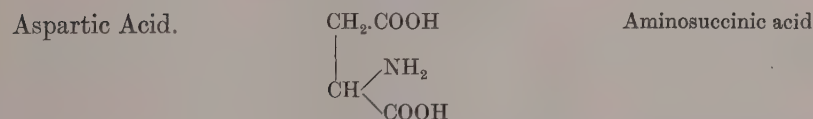
Condensed Amino-Acids



Diamino-Acids



Dicarboxylic Acids



OTHER CONSTITUENTS OF THE PROTEIN MOLECULE

When we add together the total amino-acids obtainable by the acid disintegration of any given protein, a considerable proportion of the original protein is often unaccounted for. This remainder must have a greater content in hydrogen and oxygen than the amino-acids enumerated above, and it has been suggested that among the missing unascertained constituents of proteins may be hydroxyamino-acids, of which serine would form one of the lowest members. The isolation of such substances would present considerable interest, in that it would supply the intermediate stages between the constituent groups of the protein molecule and the carbohydrates, the first product of assimilation by living organisms. Only one such intermediate body has so far been isolated, namely, glucosamine, $\text{CH}_2\text{OH}(\text{CHOH})_3\text{CHNH}_2\text{CHO}$, an amino-derivative of glucose. Both egg-white and serum contain proteins belonging to the class of mucoids, ovomucoid and serum mucoid, each of which yields on acid hydrolysis from 16 to 30 per cent. glucosamine. By our ordinary methods it is impossible to prepare a specimen of either egg albumin or serum albumin which is entirely free from this carbohydrate amino-derivative.

THE BUILDING UP OF THE PROTEIN MOLECULE

By simple hydrolysis the protein molecule may be broken down into a large number of amino-acids. Analyses of various proteins show that these amino-acids are present in different proportions in the individual proteins, so that in many cases a large number of identical amino-acid groups must be present in the protein molecule with smaller numbers of other groups. In endeavouring to form an idea of the manner in which the amino-acids can be linked together into one gigantic molecule, Hofmeister first put forward the idea that the linkage follows the general formula :



which is now called the peptide linkage.

This theory of the constitution of proteins was supported by the fact that only a small proportion of the NH_2 groups present in the separated amino-acids exist free in the protein molecule. By the action of nitrous acid the NH_2 groups are split off and replaced by OH. When proteins are treated with nitrous acid only a small proportion of the total nitrogen is split off in this way. The linking of the amino groups must therefore take place by means of the nitrogen, *i.e.* by NH groups. Synthetic experiments have fully confirmed this hypothesis. In 1883 Curtius obtained a substance giving the biuret reaction, the so-called 'biuret base,' by the spontaneous polymerisation of glycine ester. This base has been shown to consist of four glycine molecules arranged together in an open chain. The clue to the structure of this base was given by Fischer, who has devised a number of ingenious methods for combining together two or several amino-acids of any character. Thus from two molecules of glycine we may obtain the compound glycyglycine, as follows :



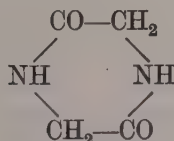
These compounds have been designated by Fischer as *peptides*, to signify their close connection with the peptones produced by the agency of digestive enzymes on the proteins. He distinguishes di-, tri-, tetra-, &c., or polypeptides according to the number of individual amino-acids taking part in

the formation of the compound, *e.g.* alanyl leucine, glycyl tyrosine, dialanyl cystine, dileucyl cystine, leucyl pentaglycyl glycine, and so on. The last named would be built up out of one molecule of leucine, and six molecules of glycine. By proper methods Abderhalden built up a very large molecule containing eighteen constituent amino-acids. The higher polypeptides closely resemble the peptones. Most of them, even if derived from relatively insoluble amino-acids, are soluble in water, insoluble in absolute alcohol. They dissolve in mineral acids and in alkalies, with the formation of salts, thus resembling in their behaviour the amino-acids. They have a bitter taste, although the amino-acids from which they are formed have a slightly sweet taste, in this way again resembling the natural peptones. The higher members of the series give certain reactions, such as the biuret reaction, which are regarded as characteristic of peptones, and like the latter are precipitated by phosphotungstic acid. Their behaviour with trypsin depends on the optical behaviour of the amino-acids from which they are formed. If synthesised from the amino-acids identical with those occurring in the disintegration of natural proteins, they resemble the peptones in undergoing hydrolysis and disintegration into their constituent amino-acids. Trypsin however has no influence on polypeptides compounded of the inactive amino-acids, or of the amino-acids which are the optical opposites of those which form the constituents of normal proteins. Though most of the amino-acids which occur naturally are lævo-rotatory, the polypeptides formed from them are generally strongly dextro-rotatory.

Thus in the building up of the protein molecule there is an almost indefinite coupling up of numerous amino-acid groups, the connecting element in each case being the nitrogen. Of the two or more possible optical isomers of each amino-acid containing more than two carbon atoms, only one is made use of for this purpose. A still further flexibility in its reactions to its environment is conferred on the protein molecule by changes occurring with great readiness in the intramolecular grouping of its constituent atoms. If we take the simplest member of the class of dipeptides, glycyl glycine, its usual formula is:

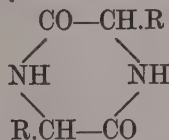


There is the further fact that union between two amino acids readily occurs by condensation to form a *diketopiperazine*. Thus from glycine we get, by elimination of water,



Diketopiperazine or glycine anhydride.

and, similarly, from any other two amino acid molecules we get corresponding diketopiperazines of the type:



Abderhalden has given grounds for the belief that such linkages also occur in the union of the amino acids to form the protein molecule, *e.g.* the fact that proteins yield a proportion of oxamide on oxidation. If we

consider that perhaps some hundred of the amino-acid groups may go to making up a single protein molecule, it is possible to form some conception of the enormous variability in reaction possible to such a compound.

THE CONSTITUTION OF DIFFERENT PROTEINS

All the proximate constituents of the main protein molecule, so far as we know, are amino-acids. Of these the following have been isolated, namely,

	Serum albumin.	Egg albumin.	Edestin (hemp seeds).	Gladin.	Caseinogen.	Globin.	Salbumin.	Salbumin.	Gelatin.	Keratin (from horse hair).	Zeln.
Glycine.	0	0	3.8	0.9	0.45	0	0	—	25.5	4.7	0.0
Alanine	2.7	8.1	3.6	2.7	1.85	4.2	—	—	8.7	1.5	9.8
Serine	0.6	—	0.33	0.12	0.5	0.6	7.8	—	0.4	0.6	1.0
Amino-valerianic acid	—	—	present	0.3	7.93	—	4.3	—	—	0.9	—
Leucine	20.0	7.1	20.9	6.0	9.7	29.0	0	—	7.1	7.1	19.6
Proline.	1.0	2.25	1.7	2.4	7.63	2.3	11.0	—	9.5	3.4	9.0
Hydroxyproline	—	—	2.0	—	0.23	1.0	—	—	14.1	—	—
Glutamic acid	7.7	8.0	6.3	36.5	21.77	1.7	—	—	5.8	3.7	26.2
Aspartic acid.	3.1	1.5	4.5	1.3	1.77	4.4	—	—	3.4	0.3	1.7
Phenyl alanine	3.1	4.4	2.4	2.6	3.88	4.2	—	—	1.4	0	6.6
Tyrosine	2.1	1.1	2.1	2.4	4.5	1.5	—	—	0.01	3.2	3.6
Tryptophane.	present	present	present	1.0	1.50	present	—	—	—	—	0.0
Cystine.	2.3	0.2	0.25	0.25	?	0.3	—	—	—	10+	—
Lysine	—	2.15	1.0	0.	7.62	4.3	0	12.0	5.9	1.1	0.0
Arginine	—	2.14	11.7	3.4	3.81	5.4	87.4	58.2	8.2	4.5	1.6
Histidine	—	—	1.1	1.7	2.5	11.0	0	12.9	0.9	0.6	0.4
β -hydroxy-glutamic acid.	—	—	—	—	10.0	—	—	—	0.0	—	—

glycine, alanine, amino-valerianic acid, leucine, isoleucine, proline, hydroxyproline, serine, phenyl alanine, glutamic acid, β -hydroxyglutamic acid, aspartic acid, tyrosine, tryptophane, cystine, lysine, histidine, and arginine.

The question now arises whether all the varieties of protein owe their peculiarities to the presence of different amino-acids, or whether the greater number of the amino-acids above mentioned are present in all proteins, the differences between the latter being determined by differences in the arrangement and relative amounts of these proximate constituents. A large number of analyses of various proteins have been made by Abderhalden, Osborne, Dakin and others, utilising the methods for the isolation of amino-acids devised by Fischer and by Dakin. The constitution of some representative proteins as determined in this way is given in the Table above.

These results show that all the proteins contain a very considerable proportion of the total number of amino-acids which have as yet been isolated from acid digests of proteins. The differences in various proteins cannot therefore be determined by qualitative differences in their constituent molecules, but must depend on the relative amounts of the amino-acids which are present and on their arrangement in the whole molecule. As regards relative amounts of amino-acids we find very striking variations. Thus glutamic acid, which forms 8 per cent. of egg albumin and only 1.7 per cent. of globin (derived from hæmoglobin), amounts to 36.5 per cent. in gliadin, the protein extracted from wheat flour. Striking differences are also noticeable in the relative proportions of the diamino-acids and bases, the so-called hexone bases. Whereas in casein they form about 12 per cent. of the total molecule, in globin they form about 20 per cent.; and in the protamines,

salmin and sturin, about 85 per cent. of the total molecule consists of these bodies. On this account the two last-named proteins have a strongly basic character. From these figures it is evident also that certain of the amino-acids must occur many times over in the protein molecule. Thus in globin, if we assume the presence of one tyrosine molecule, there must be at least thirty-two leucine and ten histidine molecules. On these data the minimal molecular weight of hæmoglobin would come out at about 14,000, a figure which agrees with that derived from a study of the amounts of sulphur and iron respectively in its molecule.

THE CLASSIFICATION OF PROTEINS

It is possible that in the future, when we know all the disintegration products of the various proteins and the manner in which they are arranged in the molecule, the classification of these bodies will be based on their constitution. At the present time it is impossible to make any classification on such a basis, since the necessary knowledge is wanting, and we have therefore to use a purely artificial classification, such as that adopted by the Chemical and Physiological Societies in 1907, based chiefly on the solubilities of the various proteins in water and salt solutions. We shall here only indicate the characters of the main groups into which proteins are conventionally divided, and leave the closer study of the individual proteins to be dealt with in connection with the organs or tissues in which they are found.

(1) THE PROTAMINES. These occur in the body only in combination with other groups. They are obtained from the ripe spermatozoa of certain fishes, where they are in combination with nucleic acid. They are characterised by the very large amount of bases in their molecule, amounting to 85 per cent. of the total substance. It was formerly thought by Kossel that the protamines contained only diamino-acids and bases, but later it was shown that a small proportion of mono-amino-acids may also be obtained from their disintegration (*v.* Salmin, Table, p. 60). On account of their constitution they possess strongly basic characters and form well-marked salts, *e.g.* sulphates and chlorides, as well as double salts with platinum chloride. They contain no sulphur and do not coagulate on heating.

(2) HISTONES. This class of proteins, like the protamines, only occurs in combination with other groups, such for instance as nuclein and hæmatin. They may be obtained from red blood corpuscles, where they form the globin part of the hæmoglobin molecule, or from the leucocytes of the thymus gland, or from the spermatozoa of fishes. The histones are precipitated from their watery solutions by addition of ammonia, but are soluble in excess of this reagent. In the presence of salts they are coagulated on boiling. With cold nitric acid they give a precipitate which dissolves on warming, but is thrown down again on cooling. The most characteristic feature of this class of bodies is the high proportion of diamino-acids and bases contained in their molecule.

(3) ALBUMINS. These are soluble in pure water and are precipitated by complete saturation with ammonium sulphate or zinc sulphate.

Egg Albumin forms the greater part of the white of egg. It gives the ordinary protein tests, coagulates on heating at about 75° C., and is precipitated from its solutions if shaken with a drop of dilute acetic acid in excess of ether. It is lævo-rotatory, its specific rotatory power being -35.5° .

Serum Albumin occurs in large quantities in the blood plasma, serum,

lymph, and tissue fluids of the body. It coagulates at 75° C., and is distinguished from egg albumin by its greater specific rotatory power, — 56°, and by the fact that it is not precipitated by ether and sulphuric acid. Some vegetable proteins belong to this class, *e.g.* the *leucosin* of wheat.

(4) **GLOBULINS.** These bodies are insoluble in pure water and require the presence of a certain amount of neutral salt to dissolve them. They are precipitated from their solutions by complete saturation with magnesium sulphate or by half-saturation with ammonium sulphate. The chief members of this class are :

Crystallin, obtained from the crystalline lens by passing a stream of carbon dioxide through an aqueous extract of this body.

Serum Globulin or *Paraglobulin*, a constituent of blood plasma and blood serum.

Fibrinogen, which occurs in blood plasma and is converted into fibrin when the blood clots.

Paramyosinogen, a normal constituent of muscle.

Midway between these two groups may be placed the muscle protein, *myosin* (or *myosinogen*) which, though soluble in pure water, resembles the class of globulins in the ease with which it is precipitated by the addition of neutral salts.

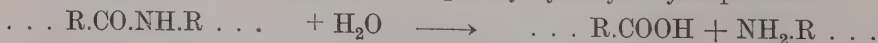
In addition to the members of the globulins named above and derived from the animal body, proteins allied to this class form an important constituent of plants, and are found in large quantities in many seeds used as articles of food. These are vegetable globulins. Prominent members of the group are the *edestins*, which may be obtained from hemp seeds, cotton seeds, and sunflower seeds, *zein* from maize, *legumin* from beans.

(5) **GLIADINS**, contained in cereals and soluble in dilute alcohol.

(6) **GLUTELINS**, also obtained from cereals and soluble in weak alkalies.

(7) **DERIVATIVES OF PROTEINS.** When proteins are subjected to the action of superheated water or steam, heated with acids, or acted on at the body temperature by certain enzymes, *e.g.* pepsin, trypsin, or papain, they undergo a disruptive change which is attended by the addition of a number of molecules of water to the protein molecule (hydrolysis). This action, when carried to its end, results in the production of the amino-acids which we have already dealt with.

These hydrolytic changes proceed by a series of stages, so that the intermediate products still present many of the protein reactions. These derived proteins are divided into three groups, *metaproteins*, *proteoses* and *peptones*. The formation of these intermediate products is especially marked with the proteolytic enzymes. Pepsin, the enzyme of the gastric juice, with hydrochloric acid for example, only breaks down the protein molecule into smaller, but still quite large molecules, the proteoses and peptones. It does not liberate any amino-acids. Trypsin also gives rise to both proteoses and peptones as intermediate products. In both cases, the peptide linkages are attacked, since equal numbers of NH₂ and COOH groups become free. The action of these enzymes on proteins is in fact closely analogous to the action of diastase on the great polysaccharide molecule of starch, inasmuch as it results in the production of a number of derivatives of progressively diminishing molecular weight and complexity by a hydrolytic process :—



The protein molecule is distinguished by the variety of the groups which enter into its formation, and this heterogeneous character of

the molecule renders possible a much greater variety of intermediate products than we find in the starches. Thus a protein molecule may consist of the groups, A, B, C, D, E, F, G, H, &c. When hydrolysis occurs it may result in the immediate splitting off, say, of part of group A, while the residue breaks up into a series of proteoses whose composition may be represented as ABF, ABC, DFG, BDEF, &c. With further hydrolysis these groups are broken into still smaller ones, and the penultimate stages of the hydrolysis will be polypeptides similar to those which have been synthesised by Fischer from the ultimate products of protein hydrolysis. No sharp dividing line can be drawn between the metaproteins, proteoses, peptones, and polypeptides. Of the last group we have already seen that the higher members give the biuret reaction as well as the other protein reactions, if the necessary groups, *e.g.* tyrosine, tryptophane, are present in the molecule. The proteoses and peptones are however ill-defined bodies. We have at present no satisfactory means of isolating the different members of these groups and obtaining them in a state of chemical purity. Their classification is therefore, like that of the proteins generally, a conventional one, depending on their solubilities and their precipitability by neutral salts, especially ammonium sulphate. Both proteoses and peptones give the xanthoproteic and Millon's reactions common to all proteins and, like these, are precipitated by such reagents as mercuric chloride, potassio-mercuric iodide, or phosphotungstic acid. They give the biuret reaction. Their solutions can be boiled without undergoing coagulation. Many of them may be thrown down from their solutions by absolute alcohol, but are not rendered insoluble even by prolonged standing under the alcohol. The characters of the different members of these groups will be considered at greater length when dealing with the changes undergone by the proteins during the process of digestion. At present we may merely summarise the distinguishing features of the three classes.

(a) *Metaproteins.* These are amongst the early products of hydrolysis of the proteins and are little less complex than the proteins from which they are derived.

Acid Albumin or *Acid Metaprotein* is formed by the action of warm dilute acids or of strong acids in the cold on any of the preceding bodies. If a weak alkali be added so as nearly to neutralise the solution of acid metaprotein, this latter is precipitated. If the precipitate be suspended in water and heated, it is coagulated and becomes insoluble in dilute acids or alkalies.

Alkali Albumin or *Alkaline Metaprotein* is formed by the action of strong caustic potash on white of egg or on any other protein, or by adding alkali in excess to a solution of acid metaprotein. It is precipitated on neutralisation of its solution.

Albumins, globulins, and metaproteins are often associated together as the coagulable proteins, since they may be thrown down entirely from their solution on boiling in very slightly acid medium in the presence of neutral salts.

(b) *Proteoses, e.g. albumose* from albumin, *caseose* from casein, *elastose* from elastin. All of these are precipitated from their solutions on saturation with ammonium sulphate. In the presence of a neutral salt they give a precipitate on the addition of nitric acid. This precipitate is dissolved on heating the solution, but reappears on cooling. All, with the exception of heteroalbumose, are soluble in pure water, and all are soluble in weak salt solutions or dilute acids or alkalies. They are slightly diffusible through animal membranes.

(c) *Peptones, e.g. fibrin peptone, gluten peptone.* These are all soluble

in pure water, diffuse fairly readily through animal membranes, but otherwise give the same reactions as albumoses. From the latter class peptones are distinguished by the fact that they are not precipitated on saturation of their solutions either in acid or alkaline reaction with ammonium sulphate or any other neutral salt. Many of them are soluble in alcohol.

(8) CONJUGATED PROTEINS. Various complex bodies which play an important part in building up cells and in the vital processes of the body make up this group of compounds. They resemble one another only in the fact that in each of them a protein radical is combined with some other body, often spoken of as the *prosthetic* group.

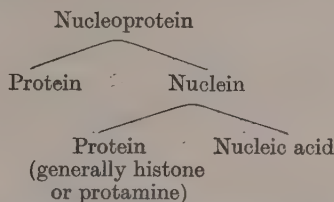
(a) *The Phosphoproteins.* In this class may be included a number of substances of very diverse properties, which however resemble one another in containing phosphorus as an integral part of their molecule. The phosphoproteins have markedly acid characters. They are insoluble in pure water, easily soluble in alkalis and ammonia, from which the original body is thrown down again on addition of acid. Their solutions in alkali are not coagulated by heating. To this class belong *caseinogen*, the chief protein of milk, *vitellin*, the main protein in the yolk of egg, and the vitellins in the eggs of fishes and frogs. The vitellins are generally associated with a large amount of lecithin. The phosphoproteins differ from the nucleoproteins, which also contain phosphorus, in that they are readily decomposed by dilute caustic alkali with the liberation of phosphoric acid, and do not contain purine bases. The phosphorus of the nucleoproteins is not split off by alkali (1 per cent.) and on hydrolysis the nucleic acid constituent gives rise to purine bases.

(b) *Chromoproteins.* Of this class, consisting of a colouring matter combined with a protein, the most important is *hæmoglobin*. This substance, which is the red colouring matter of the red corpuscles of the blood and plays an important part in the processes of respiration, acting as an oxygen carrier from the lungs to the tissues, is composed of the protein, globin, united with an iron-containing body, hæmatin. Oxyhæmoglobin contains from 4–5 per cent. hæmatin ($C_{32}H_{32}N_4O_4Fe$). It is easily crystallisable, and its physical and chemical characters have therefore been more precisely determined than is the case with most other members of the group of conjugated proteins. We shall have to deal more fully with its properties in the chapters on Blood and Respiration.

(c) *The Nucleoproteins.* These are formed by the combination of a phosphorised organic acid, *nucleic acid*, with a protein which may belong to any of the classes we have enumerated above. Some of the best-marked members of this group consist of compounds of nucleic acid with basic histones or protamines. The combination between protein and the prosthetic group seems to take place in two stages. If a nucleoprotein be subjected to gastric digestion, a large amount of the protein goes into solution as proteose or peptone, leaving an insoluble remainder. This precipitate is not however nucleic acid, but still contains a protein group, the compound being spoken of as *nuclein*. From the latter nucleic acid can be split off by heating with strong acids or other means. The nucleoproteins are soluble in water and salt solutions, and are easily soluble in dilute alkalis. They have acid characters and are precipitated by the addition of acids. The nucleins, on the other hand, are insoluble in water and salt solutions, but are easily dissolved by dilute alkalis. The nucleins and nucleoproteins form the chief and invariable constituent of cell nuclei. They may be therefore prepared from the most diverse organs. The heads of the spermatozoa of the salmon consist entirely of nuclein. Miescher and Schmiedeberg found that the nuclein obtained from this source contained 60.5 per cent. nucleic acid and

35-56 protamine, and was in fact a nucleate of protamine. The nuclein derived from the spermatozoa of echinoderms has been found to be a compound of nucleic acid and histone. From organs rich in cells, such as the thymus and the pancreas, and from nucleated red blood corpuscles, nucleoproteins may be obtained which can be broken down into nuclein and protein, the nuclein again being composed of a protein residue with nucleic acid.

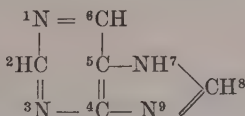
The relation of the two portions of the nucleoprotein may be represented by the following schema:



By various means, all of which involve hydrolysis, the nucleic acid may be broken up into its proximate constituents. These differ according to the source of the nucleic acid. Whatever the source, the disintegration products belong to closely allied groups of substances. These may be grouped as follows:

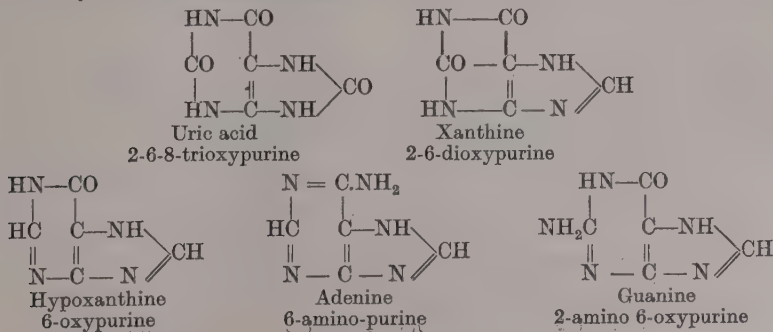
(1) Phosphoric Acid. The proportion of phosphorus varies within but narrow limits in the different nucleic acids, the average being about 10 per cent. It is probable that the phosphoric acid represents, so to speak, the combining medium for the groups contained in the nucleic acid molecule, as is the case with the various groups which make up the lecithin molecule.

(2) The Purine Bases. Among the products of disintegration of nucleic acid we find constantly one of the bases *adenine*, $\text{C}_5\text{H}_5\text{N}_3$, and *guanine*, $(\text{C}_5\text{H}_5\text{N}_3\text{O})$. These substances, with the products of their oxidation, *xanthine*, $\text{C}_5\text{H}_4\text{N}_4\text{O}_2$, *hypoxanthine*, $\text{C}_5\text{H}_4\text{N}_4\text{O}$, have long been known to be closely allied to uric acid, $\text{C}_5\text{H}_4\text{N}_4\text{O}_3$, but their true relationships have been thoroughly known only since the researches of Fischer on this group. According to Fischer they can be all regarded as derivatives of the body purine:

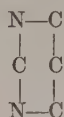


Each group in this purine ring is generally designated with a number indicated in the structural formula, in order that it may be possible to represent the position of any substituted groups in its derivatives.

The relation of xanthine, hypoxanthine, guanine, and adenine to uric acid is shown by the following formulæ:

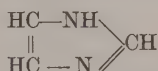


Closely allied to this group of bodies are the active constituents of tea, coffee, and cocoa, namely *caffeine*, which is *trimethyl dioxypurine*, and *theobromine*, which is *dimethyl dioxypurine*. From the structural formulæ given it will be seen that the purine radical contains two nuclei. The nucleus:



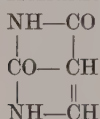
is spoken of as the pyrimidine nucleus.

The other is the radical which we have met with already in histidine, a disintegration product of proteins, namely *iminazol*:

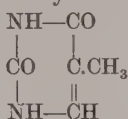


Besides the purine bases proper, we find among the disintegration products of nucleic acid a series of bases derived from the pyrimidine ring. These are uracil, thymine, and cytosine.

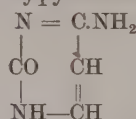
URACIL, 2-6-dioxy-
pyrimidine,



THYMINE,
5-methyl uracil,



CYTOSINE, 6-amino-2-
oxypyrimidine,



In addition to these two groups of compounds, the nucleic acids also contain a carbohydrate. It seems probable that in animal nucleic acids this is a hexose, whilst in those of vegetable origin it is a pentose, though an exception is to be noted in pancreas nucleic acid, which is said to yield a pentose. We may say that in general vegetable and animal nucleic acids comprise respectively the following units:

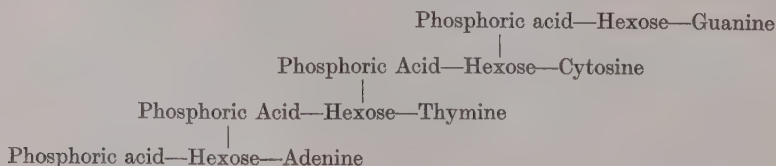
Animal.

Phosphoric acid.
Hexose.
Adenine and guanine.
Cytosine and thymine.

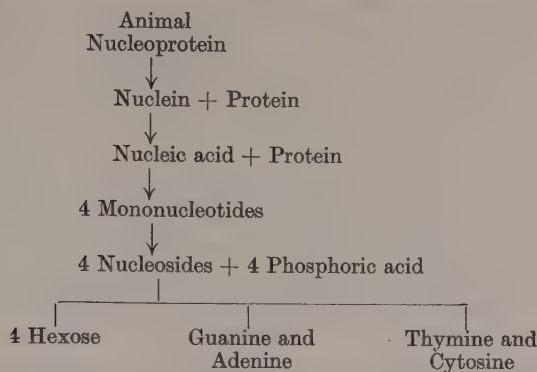
Vegetable.

Phosphoric acid.
Pentose.
Adenine and guanine.
Cytosine and uracil.

The researches of Levene and of others have thrown light on the manner of combination of these groups in the molecule of nucleic acid. It appears that each purine or pyrimidine group is combined with a carbohydrate to form what is called a 'nucleoside.' Each nucleoside is attached to a molecule of phosphoric acid, this complex being named a 'nucleotide' and representing a nucleic acid in its simplest form. In general nucleic acids are tetranucleotides, in which four mononucleotides are linked together, possibly through the phosphoric acid molecule of one and the carbohydrate of the next. Thus a tetranucleotide would have the structure



The degradation of nucleoprotein may be rendered clearer by the following scheme :



(d) *The Glycoproteins.* In the glycoproteins the prosthetic group is represented by a carbohydrate radical, generally containing nitrogen, such as glucosamine or galactosamine. They are split into their two constituents, protein and carbohydrate radical, on prolonged boiling with dilute mineral acids or by the action of alkalis. They may be divided into the two main groups, *viz.* : mucins and mucoids.

The *mucins* play a large part in the animal kingdom as protective agents. They form the slimy secretion which covers the inner surface of the mucous membranes and the outer surface of many marine animals and is secreted either by the goblet cells of the epithelium or by special groups of cells collected together to form a mucous gland. They may be precipitated from their solutions or semi-solutions by the addition of acids, and after precipitation need the addition of alkalis for their re-solution. They are not coagulable by heat. The presence of their protein moiety causes them to give the various typical protein tests, such as the xanthoproteic, Millon's, the biuret reaction, and so on. Prolonged boiling with acids splits the molecule, with the production of acid metaprotein and albumoses and glucosamine. From the mucin of frogs' eggs a similar treatment results in the production of galactosamine.

With the mucins may be classified certain bodies which have been derived from ovarian cysts, namely, *pseudomucin* and *paramucin*. Pseudomucin occurs as a constituent of the colloid material from ovarian tumours. It forms slimy solutions which do not coagulate by heat and are not precipitated by acetic acid. It is precipitated by alcohol, the precipitate being soluble in water even after standing a long time under the alcohol. On boiling with acid it gives a reducing substance. Paramucin differs from the above in reducing Fehling's solution before boiling with acids. Otherwise it resembles pseudomucin. Leathes, in investigating this body, isolated from it a reducing substance which apparently was an amino-derivative of a disaccharide, perhaps in combination with glycuronic acid.

The *mucoids* include a number of substances which may be extracted from various tissues by the action of weak alkalis, *e.g.* from tendons, bone and cartilage. The best studied example of this group is the *chondromucoid* which, with collagen, forms the ground substance of cartilage. Chondromucoid is especially rich in sulphur and gives protein by long treatment with weak alkali. On boiling for a short time with acid, it is decomposed into sulphuric acid and chondroitin, and this latter, on further action of the acid, is converted into a substance, *chondrosin*, which is certainly an amino-derivative of a polysaccharide containing the elements of glycuronic acid and an amino-disaccharide. *Chondroitin-sulphuric acid* is, according to

Levene and La Forge, a tetrasaccharide containing two hexosamine and two glycuronic acid units; the amino groups of the hexosamine units are acetylated and its primary alcohol groups esterified with sulphuric acid. It occurs not only in cartilage but also in bone, yellow elastic tissue, white fibrous tissue, and is a constant constituent of the amyloid substance which forms a deposit in the blood vessels and tissues as the result of syphilis or long-continued suppuration, and gives rise to the condition known as 'lardaceous disease.' Another example of this class of mucoids is *ovomucoid*, which is a constituent of egg-white. In order to prepare ovomucoid the globulin and albumin are precipitated by boiling diluted egg-white. From the filtrate ovomucoid can then be thrown down by alcohol. A similar body has been prepared from blood serum. Both these mucoids yield a large amount of reducing substance on hydrolysis. Thus from 100 grammes of ovomucoid it is possible to prepare 30 grammes of glucosamine.

(9) THE ALBUMINOIDS OR SCLERO-PROTEINS. Under this heading are grouped a number of diverse substances which play an important part in building up the framework of the body. Their value as skeletal tissue seems to be determined by their insoluble character. On this account it is practically impossible to purify them. In every case we can simply take the residue of a skeletal tissue which is left after extraction of the soluble constituents. When broken down by the action of strong acids, they yield a series of disintegration products which are included among those we have already studied as the disintegration products of proteins. Their difference from the proteins which are employed in metabolism for their nutritive value is probably caused by the presence of certain polypeptides which offer considerable resistance to the action of digestive enzymes. This class plays the part in the animal economy which in the vegetable kingdom is filled by the anhydrides of the hexoses and pentoses, *e.g.* the celluloses, lignin, the pentosanes, &c. *Collagen* forms the main constituent of white fibrous tissue and the ground substance of bone and cartilage. It is insoluble in water and is not digested by trypsin. Under the action of acids or when subjected to prolonged boiling with water, especially under pressure, it is converted into *gelatin*, which is soluble in hot water, forming a colloidal solution liquid at high temperatures, but setting to a jelly when cold. When subjected to acid hydrolysis it gives a series of amino-acids from which tyrosine and tryptophane are wanting. On this account gelatin does not give any reaction either with Millon's reagent or with glyoxylic acid. On the other hand, there is a preponderance of such groups as glycine and phenyl alanine. Gelatin is precipitated by tannic acid, but not by acetic acid. It is dissolved with hydrolysis by gastric juice or by pancreatic juice, whereas collagen, its anhydride, is unaffected by the latter. On prolonged boiling in water it is converted into a modification which does not form a jelly on cooling. Under the action of formaldehyde it is converted into an insoluble modification which does not melt on warming.

Reticulin. This name has been applied to the tissue which forms the supporting network of adenoid tissue, and has also been prepared from the spleen, liver, and kidneys, and from the mucous membrane of the intestine. It differs from collagen in resisting digestion by gastric juice, and also in containing phosphorus in organic combination. According to Halliburton there is no essential difference between reticulin and collagen.

The *Keratins* are produced by the modification of epithelial cells and form the horny layer of the skin as well as the main substance of hairs, wool, nails, hoofs, horns and feathers. They are distinguished by their insolubility in water, dilute acids or alkalies, and in the higher animals

pass through the alimentary canal unchanged. Although differing in their elementary composition according to the tissue from which they are prepared, they are all distinguished by the very large amount of sulphur present in their molecule. The greater part of this sulphur is in the form of cystine, of which as much as 10 per cent. can be extracted from keratin. They also yield, on acid hydrolysis, tyrosine in larger quantities than is the case with the ordinary proteins.

Neurokeratin, which forms the basis of the neuroglial framework of the central nervous system, must be grouped by its general behaviour as well as by its origin with the keratins. It resembles the other members of this class in its insolubility and in its high content in sulphur. It is extracted from nervous tissues by boiling these with alcohol and ether, and then submitting the tissue to prolonged tryptic digestion which leaves the neurokeratin unaffected.

Elastin forms the elastic fibres of the connective tissues. Elastin is insoluble in water, alcohol or ether, or in dilute acids and alkalis. It is slowly dissolved on *prolonged* treatment with gastric juice, but is practically unaffected in the alimentary canal. It gives the xanthoproteic and Millon's tests.

Other members of this group are *fibroin*, which forms the main substance of silk; *spongin*, the horny framework of sponges; *conchiolin*, the ground substance of shells; and perhaps the amyloid substance which we have already mentioned in connection with the mucoids. All these sclero-proteins present considerable differences in their qualitative and quantitative composition in amino-acids.

We have finally to mention a miscellaneous collection of bodies which are allied to the proteins and are distinguished by their extreme insolubility. They are often designated as *albumoids*. Of their composition we know practically nothing. Under this name are grouped such substances as those forming the *membrana propria* of glands and the sarcolemma of striated muscle, the albumoid of the crystalline lens, the ground material of the chorda dorsalis, the organic basis of fish scales, and many similar substances. In every case the substance is characterised necessarily according to its place of origin, little or nothing being known as to its chemical composition.

SPECIFICITY OF PROTEINS. Although certain proteins may appear to be identical so far as ordinary chemical and physical properties, and even so far as chemical analysis is concerned, they are not necessarily identical in their biological properties. For example, casein from cow's milk and casein from goat's milk, or egg albumin from hen or duck, have certain specific properties by which they are distinguished from one another. This can be shown by *anaphylactic reactions* (v. Chapter XXXVIII.). Thus if a guinea-pig is sensitised to hen-egg albumin, administration of egg albumin from another species is not followed by any effects, whereas an extremely small injection of the hen albumin promptly causes death from anaphylactic shock. There is thus a species specificity with proteins which is not seen with other biochemical constituents.

Dudley and Woodman have shown that this is in all probability due to the fact that in the different species there are slight differences in the *arrangement* of the constituent amino acids in the protein molecule. Thus if in one species we have the amino acids A, B, C, D, E . . . arranged in that order, we should have a stereochemically different molecule if the arrangement were B, D, A, C, E These species differences are of great importance in connection with the subject of immunity; they also explain why, in the construction of protein in the body, the protein taken as food must first be thoroughly broken down into its constituent amino-acids.

THE MATERIAL BASIS OF THE BODY

CHAPTER V

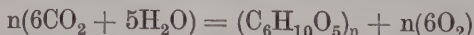
THE MECHANISM OF ORGANIC SYNTHESIS

THE ASSIMILATION OF CARBON

THE building up of protoplasm from the material which is available at the earth's surface must be an endothermic process. The food presented to the plant contains the necessary elements, but as a rule in a state of complete oxidation. The energy of the living plant, as of animals, is derived almost entirely from the oxidation of its constituents. The building up of unorganised into organised material must therefore be effected at the expense of energy supplied from without. The source of this energy is the sun's rays. The machine for the conversion of solar radiant energy into the chemical potential energy of protoplasm is the green leaf. Here a deoxidation of the carbon dioxide of the atmosphere takes place, with the production of carbohydrates, generally in the form of starch. The formation of starch must be regarded as the first act in the life-cycle, since this substance serves as a source of energy to the already formed protoplasm in its work of building up all the other constituents of the living cell. It is the solar energy captured by the green leaf which is utilised by all plants devoid of chlorophyll, as well as by the whole animal kingdom.

There are one or two exceptions to this statement. Thus the bacterium *nitrosomonas*, described by Winogradsky, grows on a medium devoid of all organic constituents, and derives the energy for its constructional activity from that set free in the conversion of ammonia into nitrites. The sulphur bacteria derive their energy from the decomposition of hydrogen sulphide and the liberation of sulphur or by the oxidation of sulphur to sulphates.

The organs of carbon dioxide assimilation are the chloroplasts. In a plant which has been kept for some time in the dark, or in an atmosphere free from carbon dioxide, they present no enclosed granules. Within three to five minutes after exposure to light in the presence of carbon dioxide, starch granules make their appearance within them and grow rapidly, assuming the typical laminated structure. These corpuscles take up carbon dioxide and water, and form carbohydrate and oxygen, as follows :



The whole structure of the green leaf is directed to the furthering of this process. A free supply of air to all the cells is provided by means of the stomata on the under surface of the leaf.

In view of the very small amount of carbon dioxide in the atmosphere, the extent of the assimilatory process is remarkable. One square metre of leaf of the *Catalpa* can lay on 1 gramme of solid per hour, using up for this purpose 784 c.cm. carbon dioxide. The rapidity of assimilation is increased within limits by increasing the intensity of the light falling on the plant. It is also increased by raising the percentage of carbon dioxide in the atmosphere supplied to the leaf. The optimum percentage of carbon dioxide will of course vary with the other conditions of the leaf. Taking the amount of assimilation in normal air with 0.03 per cent. carbon dioxide at 100, the assimilation

in an atmosphere containing 1 per cent. was 237, and was not augmented by raising the percentage of carbon dioxide to 7 per cent. Owing to the decomposition of the organic matter of the soil, the percentage of carbon dioxide near the ground is always greater than in the higher strata of the atmosphere—a fact which is taken advantage of by the low-growing plants and herbage. Other necessary conditions of assimilation are the presence of water and the maintenance of a certain external temperature. The absorption of the sun's rays by the leaf raises the temperature of the latter above that of the surrounding medium, and so quickens the process of assimilation.

The assimilation of carbon dioxide, the formation of starch, and the evolution of oxygen will go on in the isolated chloroplast. In the absence of chlorophyll, as in an etiolated leaf, the formation of starch will take place if the plant be supplied with a sugar such as glucose, and this conversion represents the main function of the *leucoplasts* present in all the cells of the reserve organs of plants. In the absence of chlorophyll no decomposition of carbon dioxide takes place, so that this pigment is evidently essential for the utilisation of the sun's energy. Chlorophyll may be extracted from leaves by means of absolute alcohol. A solution is thus obtained which is green by transmitted and red by reflected light, *i.e.* chlorophyll is a fluorescent substance. It presents four absorption bands, the chief being an intense band between Fraunhofer's lines B and C. If the chlorophyll is the means of conversion of the solar into chemical energy, the conversion must take place at the expense of the light which is absorbed by the pigment. One would therefore expect the process of assimilation to be most pronounced in those parts of the spectrum corresponding to the absorption bands—an expectation which has been realised by experiment. It has been found by Warburg and Negelein that relatively more of the absorbed energy is utilised from longer than from shorter wave-lengths.

The exact chemical changes effected by these absorbed rays are still undecided. There can be no doubt that an early product of the process is a hexose, which is rapidly converted into cane sugar or into starch. It was suggested by Baeyer in 1870 that carbon dioxide was reduced to formaldehyde, which later by condensation yielded sugar. We know that formaldehyde easily polymerises to form a mixture of hexoses, but for most plants formaldehyde is extremely poisonous, though certain algæ, as well as the water-plant, *Elodea*, can grow in a solution containing 0.001 per cent. formaldehyde.

One must assume, with Timiriazeff, that the function of chlorophyll in the process of assimilation is that of a sensitiser. Just as the addition of eosin to the emulsion used for coating photographic plates will render them sensitive to the red and green parts of the spectrum, *i.e.* will excite change in the silver salt when light from those parts of the spectrum falls upon it, so the chlorophyll serves as a means by which the absorbed solar energy can be utilised for the production of chemical change in the chloroplast. Attempts have been made to imitate this process outside the plant. The most recent and successful attempt is that of Baly. He considers that chlorophyll plays the part of an energy transformer by absorbing visible light and radiating at a frequency which accelerates the synthetic processes. He has produced polysaccharide and hexoses by the action of visible light on carbon dioxide solutions in the presence of various coloured powders capable of absorbing carbon dioxide, *e.g.* basic carbonates of nickel or cobalt. It is suggested that in a similar way the chloroplast provides a surface on which CO_2 can be absorbed, and also provides the colour. There is no need in this view to expect the presence of free formaldehyde in the green leaf, as it is held that at the moment of formation it would be in an active condition, in which it would condense immediately to more complex substances, notably hexoses.

Indeed, Baly's more recent work suggests that in those cases where formaldehyde can be detected, it has been formed secondarily by photochemical decomposition of the carbohydrate.

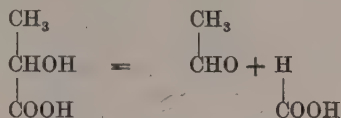
The formation of peroxides in these conditions is probably due to combination of active hydrogen with liberated oxygen. The removal of the hydrogen peroxide can be effected by a catalase, which is fairly widely distributed in plants and has been shown by Usher and Priestley to be present in the chloroplasts, whilst any formaldehyde produced is regarded as polymerising immediately it is formed.

In thus reducing certain of the stages in the assimilation of carbon to phenomena which can be imitated outside the living organism, we have made considerable strides in the 'understanding' of the process. The stage for which the vitality of the chloroplast is absolutely essential is the formation of starch from formaldehyde. Outside the body, our synthesis results in the formation of a mixture of sugars which are optically inactive. The same process, in the living cell, leads to the production of optically active sugars which are connected stereochemically and are mutually convertible one into the other, *e.g.* fructose and glucose. The derivatives of protoplasm, containing asymmetric carbon atoms, are in the same way optically active, and it seems that the asymmetry of the protoplasmic molecule conditions a corresponding asymmetry in the substance which it builds on to itself. The protoplasm furnishes, so to speak, a mould in which synthesis can result only in the production of sugars of certain definite stereochemical configurations. Baly suggests that the product, perhaps active formaldehyde, combines with the asymmetric molecule of chlorophyll and is thus polymerised asymmetrically.

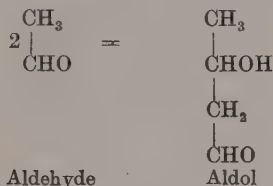
THE SYNTHESIS OF FATS

In some plants fat globules have been stated to appear as the first products of the assimilation of carbon dioxide under the influence of sunlight, but there is no doubt that as a rule the formation of fats as reserve material in seeds or fruits occurs at the expense of carbohydrates. In the higher animals too, although a variable amount of the fat of the body is derived from the fat taken up with the food, the organism can also manufacture neutral fat out of the carbohydrates presented to it in its food. The problem therefore of the synthesis of the fats is the problem of the conversion of a sugar such as glucose into glycerin and the fatty acids. Although this conversion is apparently so easily effected by the living organism, it is one which in the chemical laboratory involves considerable difficulties. On account of the fact that the higher fatty acids consist largely of oleic and stearic acids, *i.e.* acids containing eighteen carbon atoms in their chain, it has been thought that the synthesis might be brought about by the linking together of three molecules of a hexose. But sixteen out of the eighteen oxygen atoms present in the three glucose molecules would have to be dislodged in order to convert the chain into stearic acid. Moreover, although these two acids contain a multiple of six carbon atoms, a whole array of fats is found both in plants and animals which could not be derived by a simple aggregation of glucose molecules; and it is worthy of note that, of all the fatty acids which occur in nature, all those with more than five carbon atoms contain an even number of carbon atoms. Thus in milk, in addition to glycerides of the three common acids, stearic, palmitic, and oleic, we find the glycerides of caproic, caprylic, capric, lauric and myristic acids, *i.e.* acids with 6, 8, 10, 12, and 14 carbon atoms. In all cases these acids are the normal acids with straight unbranched chains. It seems probable that, in the transformation of carbo-

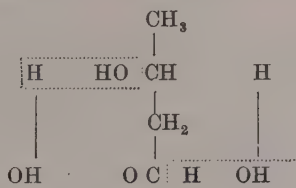
hydrate into fatty acid, the latter is built up, not by six carbon atoms but by two carbon atoms at a time. It has been suggested by Magnus Levy and by Leathes that the transformation may occur by way of lactic acid. We have seen that glucose and the sugars of analogous constitution may easily be converted into lactic acid. Lactic acid breaks down with readiness into acetaldehyde and formic acid :



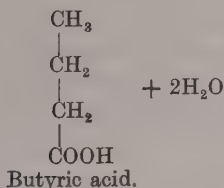
Aldehyde undergoes condensation to form aldol :



Aldol reacts with water and undergoes a shifting of its OH and H groups, in a manner with which we are already familiar as occurring in the conversion of glucose into lactic acid, forming butyric acid. We may represent the reaction in the following way, placing the water molecules opposite those groups of the aldol molecule with which they react :



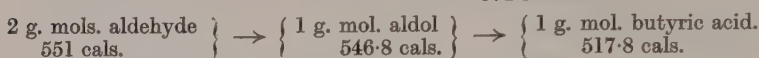
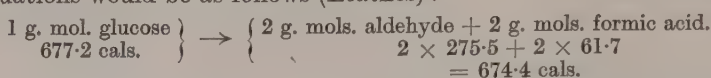
gives



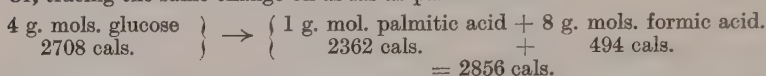
It will be seen that, although water must enter into the reaction, there is no addition of water to the aldol in order to form the butyric acid.

It has been suggested that similar reactions might account for the formation of the higher fatty acids, in which case one molecule of acetic aldehyde would be added to the fatty acid in order to build up the acid which is next highest in the series. Although certain of the higher acids have been prepared in this way, proof is still wanting that a continuous series of syntheses may be effected by the continuous addition of aldehyde. Such a hypothesis is however more probable than the direct conversion of three molecules of sugar into one molecule of stearic acid. The latter change would be associated with a very great absorption of energy, whereas a continuous building up of fatty acids, by the addition of aldehyde obtained through lactic acid from the disintegration of hexose molecules, requires only a small expenditure of energy, which could be obtained by the combustion of the formic acid formed as a by-product in the process. If we suppose that the synthesis of

the higher fatty acids from sugar is carried out in this way, the energy equations would be as follows (Leathes):

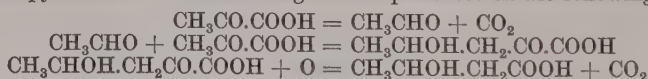


Or, tracing the same change on as far as palmitic acid:



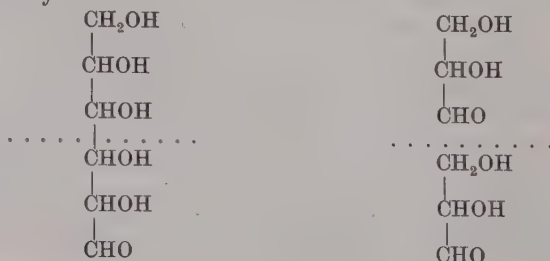
In the first stage of the synthesis, the reaction leading to butyric acid, the net result would be, supposing the formic acid to be oxidised, that some 160 calories, or nearly 25 per cent. of the whole energy, would be rendered available for other purposes. In the latter stages leading to palmitic acid, some of the energy derived from the oxidation of the formic acid would be required for effecting the synthesis, and only about 12.5 per cent. of the original amount contained in the sugar would be set free. It is worth noting that, in the butyric fermentation of sugar by micro-organisms, there is a production first of lactic acid, which then disappears to give place to butyric acid. At the same time carbonic acid and hydrogen are evolved, both gases being derived from the decomposition of the formic acid. In the process a certain amount of caproic acid is always produced, and the crude butyric acid of fermentation is used as the source from which commercial caproic acid is derived.

Attempts to produce the higher fatty acids by the condensation of successive molecules of aldehyde have so far resulted only in the production of branched chains of carbon atoms, whereas the normal fatty acids of the body are straight chains; though Raper has shown that the normal caproic acid may be formed by the condensation of aldol with itself. Miss Smedley has suggested that a more probable line of synthesis lies through pyruvic acid. *Pyruvic acid*, which may be produced in the body from lactic acid and so from carbohydrate, is fermented by yeast with the production of acetaldehyde and carbon dioxide, by means of a ferment, carboxylase. Aldehyde however combines with a molecule of pyruvic acid to form a higher keto-acid, which might either be oxidised to the fatty acid containing one carbon atom less, or might be again transformed by enzymes into an aldehyde capable of reacting with another molecule of pyruvic acid. These changes are represented in the following equations:



β -oxyacids would thus be a normal stage in the building up as well as in the breaking down of fatty acids.

The glycerol, which enters into the formation of the ordinary neutral fats, can be synthesised by both plants and animals, and there is every ground for believing that it, like the fatty acids, may be derived from carbohydrates. In the conversion of glucose into lactic acid a first step may be the formation of glyceric aldehyde:



and it is easy to understand how by a process of reduction the aldehyde is converted into the corresponding alcohol, namely, glycerol. The synthesis of the neutral fat from glycerol and fatty acid is a change which can be accomplished by many enzymes. It is one involving practically no absorption or expenditure of energy. The change is a reversible one, and we find both in plants and animals that a hydrolysis of neutral fat into fatty acid and glycerol always occurs when a transport of the fat is required, while the laying down of fat as a store of energy is always preceded by a resynthesis of the neutral fat. We shall have occasion to deal in greater detail with these questions when we have to discuss the formation and fate of the fat in the animal body.

THE FORMATION OF PROTEINS

Our knowledge of the mechanism by which proteins are synthesised in plants is still more incomplete than that of the synthesis of carbohydrates; and we are reduced in most cases to a discussion of the possible ways in which, from our knowledge of the chemical behaviour of the constituents of the protein molecule, we may conceive of its formation. We can at any rate state the problems which have to be solved and study the conditions under which the synthesis of protein is possible in plants and in animals.

We know that plants are independent of any organic food for building up their various constituents, whether carbohydrate, protein or fat, provided only that they possess chlorophyll corpuscles and so are able to utilise the energy of the sun's rays. Most plants will grow in the dark if supplied with sugar and with combined nitrogen either in the form of ammonia or of nitrates. The higher plants are especially dependent on the presence of nitrogen in the latter form, and it is on this account that the nitrifying bacteria of the soil acquire so great an importance for agriculture. From the carbon dioxide of the atmosphere or from the hexose formed by the assimilation of carbon, and from nitrogen in the form either of ammonia or nitrates, together with inorganic sulphates, the plant cell is able to build up all the various types of protein which are distributed throughout the vegetable kingdom. Our study of the disintegration products of proteins has shown that this class of bodies contains a large number of the most diverse groups, having as a common character the possession of nitrogen in their molecule, generally as an NH_2 or NH group. These disintegration products can be classified as follows:

- (a) Open chain amino-acids.
- (b) Heterocyclic compounds, including :
 - (1) Pyrrol derivatives.
 - (2) Pyrimidine derivatives.
 - (3) Iminazol derivatives.

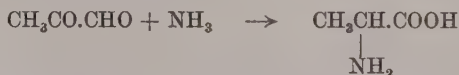
These two last groups co-exist in all the purine compounds.

- (c) Benzene derivatives.
- (d) Indol derivatives.

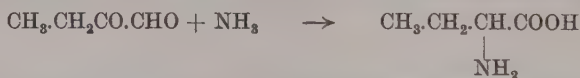
The first step in the synthesis of proteins is probably the formation of these constituent groups. Just as in digestion the protein molecule is taken to pieces with the formation of the different amino-acids, so in the synthetic action of protoplasm the reverse process of dehydration occurs, resulting in a coupling up of the different groups, as has been effected by Fischer in the case of the polypeptides. Wherever transport of protein from one part of the organism to another is necessary, the protein is carried, not in its original form, but in the hydrolysed condition of amino-acids. Thus the germination

of seeds which contain rich stores of protein is accompanied by a liberation of proteolytic enzymes within the cells of the seeds, and the breakdown of the reserve protein into its constituent amino-acids. As amino-acids it is transported into the growing tip and leaves of the seedling, analysis of the latter showing a very large percentage of nitrogen in the form of amino-acids. This is especially the case if the synthetic functions of the growing tip are hindered by interference with assimilation, as *e.g.* by keeping the plant in the dark. Under these circumstances, asparagine may form as much as 25 per cent. of the total dried weight of the seedling. In animals the greater part of the protein of the food is broken down into its constituent amino-acids in the intestine. These are absorbed and carried to the different organs of the body, where they are resynthesised, generally in different proportions from those of the original protein, into the protein specific for the organ or tissue. The same process of hydrolysis and subsequent synthesis occurs whenever the transport of protein is necessary from one organ to another. We shall later on have to discuss the possibility of synthesis of the different amino-acids in animals. We need therefore at present deal only with the possible methods by which, from the glucose or substances produced in the assimilation of carbon and from the ammonia or nitrates derived from the soil, the plant is able to make the different groups which go to the building up of the protein molecule.

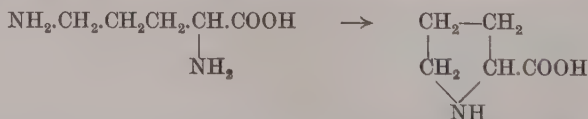
It seems to be fairly well established that sugar can be converted biochemically into lactic acid with the intermediate formation of pyruvic aldehyde. In the presence of ammonia this latter substance might form alanine, for Dakin has shown that solutions of the latter yield pyruvic aldehyde in small amount at room temperature :



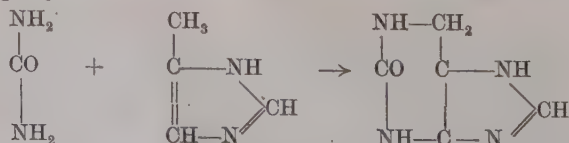
Substituted amino-acids may be considered to arise from α keto aldehydes such as might appear in the scheme of fat synthesis suggested by Miss Smedley :



Perhaps the diamino-acids such as lysine arise in the same way. The pyrrol ring of proline may be derived by intramolecular condensation from ornithine :



Glyoxals (*e.g.* pyruvic aldehyde) readily condense with ammonia yielding substances containing the iminazol ring. The purine ring may be considered to be a condensation product of urea (*i.e.* ammonia and carbon dioxide) and a glyoxaline ring, *e.g.*

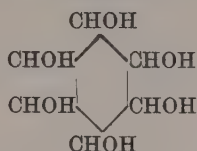


Again the pyrimidine nucleus may arise by the condensation of urea with some three-membered carbon chain such as pyruvic aldehyde.

It will be seen that we are entirely in the dark as to the routes of synthesis

of the nitrogenous constituents of plants and have been able to indicate only a few theoretical relationships of the main groups of compounds.

With regard to the formation of the aromatic constituents of the protein molecule, *i.e.* those containing the benzene and indol rings, we have at present very little indication even of the lines along which it might be possible to prosecute our researches. It has been suggested that inositol may represent some stage in the formation of the benzene ring from the open chain found in the carbohydrates. Inositol has the same formula as glucose, namely $C_6H_{12}O_6$, but is a saturated ring compound :



and may be expected to be formed as a result of polymerisation of formaldehyde. We have no evidence however of the possibility of such a formation, and the relations of this substance with the benzene compounds are by no means intimate. It is of such universal occurrence, both in plants and animals, that it is difficult to refrain from the suspicion that it may play some part as an intermediate stage between the fatty and the aromatic series.

Since plants are able to manufacture all these varied substances out of the products of assimilation of carbon and ammonia or nitrates, they must also find no difficulty in transforming one amino-acid into another, and we know that most plants can procure their nitrogen from a solution of a single amino-acid as well as from a nutrient fluid containing the nitrogen in the form of ammonia. In animals the power of transforming one amino-acid into another is probably strictly limited. So far as we know, nearly all the amino-acids utilised in the building up of the animal proteins are derived directly from those contained in the food. On the other hand, we have evidence in the animal body of synthesis of the purine bodies, and therefore of the pyrimidine and iminazol rings. The hen's egg at the beginning of incubation contains very little nuclein, nearly the whole of its phosphorus being present in the form of phosphoproteins and lecithin. As incubation proceeds these substances disappear, their place being taken by the nucleins which form the chief constituent of the nuclei of the developing chick. In the same way the ovaries and testes of the salmon are formed during their sojourn in fresh water at the expense of the skeletal muscles, especially those of the back. Here again there is a transformation of a tissue poor in purine bases into a tissue which consists almost exclusively of nucleins and protamines. Whether in this case there is a direct conversion of the monoamino-acids of the muscle proteins into the diamino-acids and bases typical of protamines, we do not know. It is more probable that only diamino-acids and bases previously existing in the muscle are utilised for the formation of the generative glands, the other amino-acids being oxidised and utilised for the ordinary energy requirements of the animal,

THE ENERGETIC BASIS OF THE BODY

CHAPTER VI

THE ENERGY OF MOLECULES IN SOLUTION

EVERY vital act involves at the same time some material alterations in the living cell and a transformation of energy. The ultimate source of the energies displayed by the animal organism is the chemical energy of the substances taken in as food. In all the changes undergone by either matter or energy in the body there is neither destruction nor creation. The living organism may therefore be regarded in one sense as a machine, that is to say, a system for the conversion of one form of energy into another. In the living cell the chemical energy of the food may undergo conversion into other forms, *i.e.* heat, work, electrical difference of potential, or it may be used for the production of other chemical substances possessing perhaps as much potential energy as or more than the foodstuffs themselves.

Protoplasm, which is the seat of all these changes in both plants and animals, is active only within fairly narrow limits of temperature, approximately between 5° and 40° C. In consistence it is slimy and wet, water forming from 70 to 95 per cent. of its bulk. No substance introduced into the protoplasm has any chemical influence on it, unless it be soluble, and the first stage in the preparation of foodstuffs for assimilation always consists in a process of solution. The sole source of energy to the body being that conveyed with the food, it follows that all the energy with which we have to deal is the energy of *molecules in watery solution*, the playground of whose activities is a jelly-like mass of colloidal material, heterogeneous yet structurally continuous. It is important therefore at the outset to inquire into the nature of this energy and the methods by which it may be measured.

OSMOTIC PRESSURE

If we place two gas jars together, mouth to mouth, as in Fig. 16, the upper jar containing hydrogen and the lower jar some heavier gas such as oxygen or carbon dioxide, within a very short time the gases will have become intimately mixed, and each jar will contain an equal amount of both gases. We say that each gas has diffused into the other, and ascribe the diffusion to the movement of the gaseous molecules. In closed vessels the rapidly moving molecules are continually impinging on the walls of the vessels and rebounding, and it is this bombardment by the gaseous molecules which is responsible for the pressure exerted by a gas on its containing walls. If we double the amount of gas in a given space, we double the number of molecules which strike a unit area of the wall in unit time, and therefore double the pressure exerted by the gas on the vessel wall. In this way we may explain the law of Boyle that the pressure of a gas is inversely proportional to its volume, or the product of pressure and volume at a given temperature

is a constant, $PV = C$, or since the energy of the molecules is proportionate to the absolute temperature, $PV = RT$, the familiar gas equation.

The molecules of substances in solution behave, *within the limits of the solution*, in a manner very similar to the free molecules of a gas. Thus, if a vessel be half filled with a 10 per cent. solution of sugar, and be then filled up by carefully pouring in distilled water, so as to form a distinct layer on the heavier sugar solution, the sugar at once begins to move upwards into the distilled water. In consequence of the resistance offered to the movement of the sugar molecules through the water, this process of *diffusion* is slow; but if the vessel be left undisturbed and free from any agitation for two or three months, the sugar will be found to spread gradually throughout the liquid, so that at the end of this time all parts of the fluid contain a uniform amount of sugar.

This process of diffusion, like that of gases, must be ascribed to a continuous translatory movement of the dissolved molecules. Since the molecules possess mass and are endowed with a velocity, they can exercise a pressure on any membrane or dividing surface which tends to hinder their free passage within the limits of the solvent. Thus if we take a pig's bladder containing a 20 per cent. solution of dextrose and immerse it in distilled water, water will pass in and distend the bladder to such an extent that it may burst from the rise of pressure in its interior. This swelling of the bladder is due to the fact that the molecules of sugar pass through it only with difficulty, whereas the water molecules pass easily. Owing to the presence of the dissolved substance, however, the number of water molecules striking the membrane in a given time will be greater on the outside than on the inside, so that water passes in at a rate which is proportional to the difference, *i.e.* to the number of sugar molecules in the solution, so causing a distension of the bladder. The uptake of water will continue



Fig. 16.

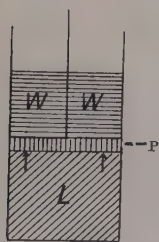


Fig. 16A.

until the pressure inside is great enough to force water out at a rate equal to that at which it enters. This pressure is called the *osmotic pressure*, and experiment shows that the osmotic pressure exerted by a solute in a given volume of solvent is the same as it would exert when confined as a gas to the same volume, *i.e.* one gramme molecule dissolved in 22.4 litres would have an osmotic pressure of one atmosphere. It is impossible however by this means to obtain the full osmotic pressure due to the presence exerted by the sugar molecules, since the bladder wall itself is not absolutely impermeable to sugar. If we imagine the sugar solution confined in a cylinder and covered with a layer of distilled water, the movement of the sugar molecules will cause them to wander from the lower to the upper part; and this process of diffusion will cease only when the concentration has become the same in all parts of the solution. Supposing however the two fluids are separated by a piston, *P* (Fig. 16A), which is 'semi-permeable,' *i.e.* allows free passage to water but not to the dissolved sugar, the solution will now exert a pressure on the piston similar to that exerted on the walls of the containing vessel, and will tend to drive it upwards. The force which it is necessary to apply to the

piston to prevent its upward movement will be the measure of the osmotic pressure of the sugar in the solution. If the piston be pushed down with a greater force, the sugar molecules alone are pressed together, since water can pass freely through the surface of the piston, and the sugar solution is therefore rendered more concentrated. Since force must be applied to the piston in order to push it down, work is done in the process, so that the concentration of any solution involves the performance of an amount of work determined by the initial and final osmotic pressure of the solution. If on the other hand a weight be applied to the piston which is less than the osmotic pressure exerted by the sugar solution, the piston with its weight will be moved upwards, water will pass through the pores of the piston, and the solution will undergo dilution until its osmotic pressure exactly balances the weight on the piston. We see that the osmotic pressure of a solution represents a certain amount of potential energy, which can be utilised in an osmotic machine, such as that represented in the diagram, for the performance of work.

The amount of work done in this way can be calculated in exactly the same way as when we are dealing with a gas. To compress a gramme molecule of any perfect gas from volume V_1 to volume V_2 requires the expenditure of work represented by $W = RT \log \frac{V_1}{V_2}$. If we take the pressures and compress from pressure p_1 to pressure p_2 , the expression will be $W = RT \log \frac{p_2}{p_1}$. To convert from natural to ordinary logarithms, we must multiply this expression by 2.303. The numerical value of R depends on the units required being 1.991 for gramme calories and 0.848 for kilogramme metres. T at 37°C . is 310°C . The equation then becomes:

$$\left. \begin{array}{l} W = 1421 \text{ gramme calories} \\ \text{or } 605.5 \text{ kilogramme metres} \end{array} \right\} \times \log \frac{p_2}{p_1}$$

To compress a fluid containing one gramme molecule of solute from osmotic pressure π_1 until it is concentrated to an osmotic pressure π_2 , would require $605.5 \times \log \frac{\pi_2}{\pi_1}$ kilogramme metres.

It must be remembered that this expression gives the work done in concentrating a solution (whatever method of concentration be applied, *e.g.* evaporation) at a constant temperature.

THE MEASUREMENT OF OSMOTIC PRESSURE. By a method differing but little from the one just sketched out, it is possible directly to measure the osmotic pressure of aqueous solutions. The improvement consists in the use of a membrane which is truly *semi-permeable*, *i.e.* which will not allow any molecules of solute to pass, but is freely permeable to the solvent. Such a membrane is provided when certain substances are precipitated in films, and one of these is copper ferrocyanide. Pfeffer conceived the idea of depositing such a semi-permeable membrane within the interstices of a clay cell. Strengthened in this way, it is able to afford a resistance to pressure, and therefore to permit of the contained fluid reaching its full osmotic pressure. For this purpose a porous jar carefully cleansed and containing a solution of sugar mixed with a little copper sulphate is dipped into a weak solution of potassium ferrocyanide. A semi-permeable membrane of copper ferrocyanide is thus produced in the pores of the filter. The tube is then fitted with a cork provided with a closed mercurial manometer and is immersed in distilled water, when it is found that water passes into the cell until the pressure within the latter is equal to the osmotic pressure of the dissolved substances. By this means Pfeffer obtained the

following results with a 1 per cent. solution of cane sugar at different temperatures :

Temp. °C.	Pressure in atmospheres.	
	Observed.	Calculated.
6.8	Atm. 0.664	Atm. 0.665
13.7	0.691	0.681
22.0	0.721	0.701
32.0	0.716	0.725
36.0	0.746	0.735

It is always possible to calculate the pressure of a gas when its nature, its mass and its volume are known. By Avogadro's hypothesis, equal volumes of gases at the same pressure contain equal numbers of molecules. On this account the molecular weight of any gas can be reckoned directly from its density. The figures obtained by Pfeffer show that the same laws apply to the osmotic pressure of substances in solution as to the pressure of gases in their free state. It is therefore possible to reckon the osmotic pressure which would be exerted by 1 per cent. sugar in solution at a given temperature.

This calculation is carried out as follows : A gramme molecule of any gas at 0° C. and 760 mm. Hg has a volume of 22.4 litres, therefore 342 grammes of cane sugar (one mole), if it could be converted into a gas at 0° C. and 760 mm. Hg, would have a volume of 22.4 litres. In Pfeffer's experiment the gramme of sugar was dissolved in 100 grammes of water, making a total volume at 0° C. of 100.6 c.c. The osmotic pressure of the sugar molecules in this solution will therefore amount to $\frac{22400}{342 \times 100.6} = 0.651$ atmosphere.

At a temperature of 6.8° the pressure would be 0.667 atmosphere, as against the observed 0.664 atmosphere.

Pfeffer's method is difficult to carry out and is not applicable to all dissolved substances, since the cupric ferrocyanide membrane is permeable for many substances, such as potassium nitrate or hydrochloric acid. Other indirect methods have therefore been applied to the comparison of the osmotic pressures of different solutions.

DETERMINATION OF OSMOTIC PRESSURE BY PLASMOLYSIS

Solutions which have the same osmotic pressure are spoken of as isosmotic. The method of plasmolysis, which we owe to the botanist De Vries, consists essentially in the comparison of the osmotic pressure of solutions with that of the cell sap of certain plant cells, and depends on the fact that the 'primordial utricle,' the layer of protoplasm enclosing the cell sap, while freely permeable to water, is impermeable to a large number of salts and other crystalloids, such as sugar. It is therefore, so far as concerns these substances, 'semi-permeable.' The cells which have been most used for this purpose are the cuticular cells on the midrib of the lower surface of the leaves of *tradescantia discolor*. If some of these cells are brought into a concentrated salt solution, which is 'hypertonic' as compared with the cell sap, water passes out of the cell into the salt solution, until the contents of the cell attain a molecular concentration equal to that of the surrounding medium. The protoplasmic layer therefore shrinks, leaving a space between it and the cell wall (Fig. 10, p. 23). If the outer solution has a smaller molecular concentration than the cell sap, water passes into the cell and causes here a rise of pressure which simply presses the protoplasm still more closely against the cell wall. If we determine the concentration of the salt solution at which the shrinkage of the protoplasm, the *plasmolysis*, just occurs, and another smaller concentration at which plasmolysis is absent, we know that the concentration of the cell sap lies between those of the two salt solutions. Thus, if plasmolysis occurs in a solution containing 0.6 per

cent. sodium chloride and is absent in a solution containing 0.59 per cent. of the same salt, the concentration of the cell sap must be about equivalent to a 0.595 per cent. NaCl solution. Solutions of different salts, in which plasmolysis just occurs, must also be isotonic with one another. Thus a 1.01 per cent. solution of KNO_3 is found to be isotonic with a 0.58 per cent. NaCl solution.

DETERMINATION BY HAMBURGER'S BLOOD CORPUSCLE METHOD.

The limiting external layer of red blood corpuscles resembles the primordial utricle of plant cells in being impermeable to a number of dissolved substances. If it be placed in a solution of smaller concentration than the corpuscle contents, it will swell up and, since it has no supporting cell wall, the increase in size may go on until the corpuscle bursts, and its contained red colouring matter, hæmoglobin, passes into solution in the surrounding fluid. If the corpuscles be then allowed to settle or be centrifuged, the fact that hæmolysis has occurred is shown by the red colour of the clear supernatant fluid. With a given sample of blood, the concentration of a potassium nitrate solution is found at which the first traces of hæmolysis occur. In order to determine the osmotic pressure of a solution, say of sugar or of sodium chloride, these are also added in various dilutions to blood corpuscles until we get solutions in which hæmolysis just occurs. These solutions will then be isotonic with the first determined potassium nitrate solutions. As an example of this method may be adduced the following results :

	Concentration of the solution in which the blood corpuscles do not lose hæmoglobin.	Concentration of the solution in which the blood corpuscles begin to lose hæmoglobin.	Mean concentration.
	Per cent.	Per cent.	Per cent.
Potassium nitrate . .	1.04	0.96	1.00
Sodium chloride . .	0.60	0.56	0.585
Cane sugar . .	6.29	5.63	5.96
Potassium iodide . .	1.71	1.57	1.64
Sodium iodide . .	1.54	1.47	1.505
Potassium bromide . .	1.22	1.13	1.17

Isotonic is not identical with isosmotic. Tonicity has reference to the action of the solution with regard to some cell membrane, and therefore involves the impermeability of the membrane to the substance or substances in solution. Thus equimolecular solutions of urea and of grape sugar would be isosmotic. Tested by the blood corpuscle method the solution of urea would be found to be isotonic with distilled water, since the outer layer of a blood corpuscle is freely permeable to urea, but not to sugar. Urea is therefore unable to exert any osmotic pressure in relation to blood corpuscles.

INDIRECT METHODS OF MEASURING OSMOTIC PRESSURE. Equimolecular solutions (of non-electrolytes) have the same osmotic pressures. Since the osmotic pressure of a solution is dependent on the number of molecules it contains in unit space, any method which will tell us the number of molecules present will also enable us to determine the osmotic pressure. Other properties of solutions which, like the osmotic pressure, are functions of the number of molecules present, are vapour tension, boiling point, freezing point. The presence of a substance in solution in water diminishes its vapour tension at any given temperature, raises its boiling point, and depresses its freezing point; and the extent of the deviation from distilled water is proportional to the number of dissolved molecules present. The determination of the rise of boiling point, though much employed by chemists, is of very little value in physiology, owing to the fact that nearly all the fluids of the body are seriously modified in character by a rise of temperature to 100° C. On the other hand, Barger has suggested an ingenious method in which the alteration of vapour tension is made the basis of a method for determining the osmotic pressure of small quantities of fluids at ordinary temperatures. In this method, drops of the fluid, the vapour tension of which it is desired to ascertain, are drawn up into a tube (1.5 mm. in diameter), so as to alternate with small drops of cane sugar solution of known content (Fig. 17). Water in a state of vapour will pass from the solution of which the vapour tension is the higher. By observing the edge of a drop under a magnification of 65 diams., it can be easily seen

whether it has grown or diminished in size. If the edge of the drop remains stationary, it shows that the vapour tension and the osmotic pressure of the two fluids are equal. A series of trials is made with different strengths of sugar solution until this equality is established. In this method only minimal quantities of material are required, and the determination of the aqueous tension is made at ordinary temperatures.

The method however which is of greatest value in physiology is the measurement of the depression of freezing point (generally represented by the Greek letter Δ).

The determination is carried out in a Beckmann's apparatus with a thermometer reading to $\frac{1}{100}^{\circ}\text{C}$. (Fig. 18). A solution freezes at a lower temperature than pure water, and the depression of freezing point is proportional to the number of molecules present. Thus the freezing point of a decimolar solution of glucose is -0.186°C ., and the same freezing point would be found for decimolar solutions of urea or of cane sugar. A molar solution (*i.e.* one containing one gramme molecule per litre, in the case of glucose 180 grammes), would have a Δ of 1.86°C . Since this has, as clearly explained, an osmotic pressure of 22.4 atmospheres, it is evident that the depression of freezing point can be converted directly into osmotic pressure by multiplying the depression by $\frac{22.4}{1.86} = 12.04$. Thus

a 1 per cent. solution of sodium chloride with $\Delta = 0.61$

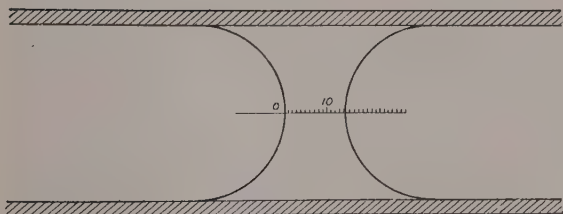
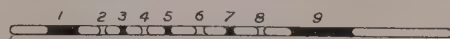


FIG. 17. Diagram to illustrate Barger's Method of Determining Osmotic Pressure. The upper figure shows the capillary tube with nine alternate drops of cane sugar and the substance under investigation.

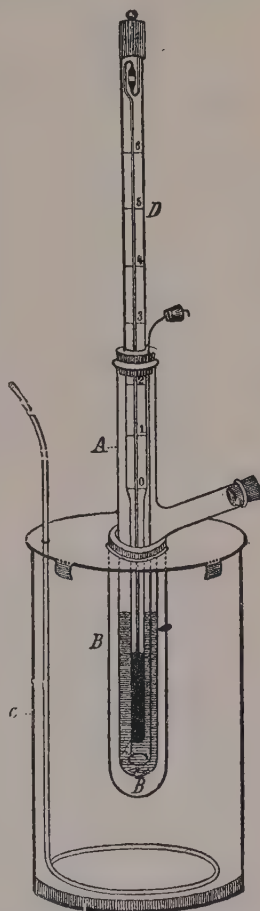


FIG. 18. Beckmann's Apparatus for Determination of Freezing Point.

will have an osmotic pressure of $0.61 \times 12.04 = 73.4$ atmospheres, while a 1 per cent. cane sugar solution with a $\Delta = .0546$ will have an osmotic pressure of 0.675 atmosphere. This method has the advantage that the fluids are in most cases in no wise altered by the process of freezing, and it can be applied to solutions containing coagulable proteins which would be irretrievably altered by any considerable rise of temperature.

OSMOTIC PRESSURE OF ELECTROLYTES. The molecular weight of NaCl is 58.5; that of glucose is 180. We might therefore expect to find that a 0.85 per cent. solution of NaCl would be isotonic or isosmotic with a 1.8 per cent. solution of glucose. Actually it is isosmotic with a glucose solution of about 3.5 per cent., whether the osmotic pressure be measured by the blood corpuscle method, by vapour tension or by estimation of freezing point. This increase in the theoretical value of the osmotic pressure, as decided from the molecular weight, is connected with

the fact that salt solutions, as well as solutions of acids and alkalies, are electrolytes, *i.e.* conduct electricity. Pure water hardly conducts a current at all, and its conducting power is little altered by the addition of sugar, but the smallest trace of salt, acid or alkali added to distilled water enormously improves its conducting power. Arrhenius has shown that the conducting power of electrolytes depends on the fact that their molecules, in the act of solution in certain fluids of which water is the chief, undergo dissociation which increases with the dilution of the solution. When a current of electricity is passed through such a solution, the positively charged ions, cations, pass to the negative pole, while the negatively charged ions, anions, pass to the positive pole. Since each charged ion as regards osmotic pressure and the related properties acts as a whole molecule, the osmotic pressure of a dilute solution of NaCl is double that of an equimolecular solution of glucose.

If the solution is one of sodium sulphate the osmotic pressure is increased three times, since this salt dissociates into two Na ions and one SO_4 ion.

Every substance in solution evidently possesses a certain amount of potential energy in the form of osmotic pressure. This pressure is independent of the nature of the substance dissolved and is determined merely by its molecular concentration and degree of ionic dissociation. It can be used as a driving force for the movement by diffusion of the molecules themselves or, by the use of appropriate mechanisms or 'machines,' for the performance of mechanical work or, as will be seen later, for the production of electrical differences of potential.

NORMAL PHYSIOLOGICAL SOLUTIONS. When vegetable cells are placed in sugar solution, it is possible to find such a concentration that the cell contents neither increase nor diminish. At this concentration the sugar solution is said to be isotonic with the cell sap. In the same way, using blood corpuscles, we may find a concentration of the sugar at which the corpuscles will neither increase nor diminish in bulk. This concentration varies according to the animal from which the corpuscles are derived. Instead of sugar we can use sodium chloride. It is then found that a 0.65 per cent. NaCl solution is isotonic with frogs' blood corpuscles, and that a 0.9 per cent. NaCl solution is isotonic with mammalian red corpuscles. Since the osmotic concentration is identical in all the cells of the body and is the same as that of the circulating blood, 0.65 per cent. and 0.9 per cent. NaCl solutions have been given the name of 'normal saline,' and are used for maintaining tissues moist when they are under experiment. Since the limiting external layer of most cells seems to resemble blood corpuscles in being impermeable to sugar and neutral salts, it might be thought that it was a matter of indifference what salts were used for making normal saline. This is not the case. It was shown first by Ringer that, if an excised frog's heart were perfused with a pure solution of 0.65 per cent. NaCl, the beats became smaller and smaller and finally ceased. On the addition of a trace of calcium salt the heart improved for a time and then went into tonic contraction, but on the addition of a trace of potassium salt the normal beats were restored.

The function of a cell is thus dependent, not only on the nature of its contents and on the osmotic pressure of the surrounding fluid, but also on the nature of the ions which are in contact with its external surface. It should be noted that it is a matter of indifference what salts of calcium or potassium are used, since it is the metallic ions themselves which are responsible for the effect. When we wish to keep a tissue alive, immersed in some solution, we employ a 'Ringer's fluid' in which sodium, potassium and calcium ions are present in the proper amounts. It is customary to add also some

sodium bicarbonate and sometimes sodium phosphate, so as to imitate the reaction of the normal body fluids and to provide a means of neutralising small amounts of acid which may be produced during the activity of the tissue under investigation. The accompanying table shows the composition of some commonly employed physiological saline solutions.

PHYSIOLOGICAL SALINE SOLUTIONS.

	Ringer (Frog).	Ringer- Locke.	Ringer- Tyrode.	Ringer- Dale.	Buffered Ringer [C. L. E.].
Water	100.0	100.0	100.0	100.0	100.0
NaCl	0.65	0.9	0.8	0.9	0.85
KCl	0.014	0.042	0.02	0.042	0.042
CaCl ₂	0.012	0.024	0.02	0.024	0.024
NaHCO ₃	0.02	0.01-0.03	0.1	0.05	—
NaH ₂ PO ₄	0.001	—	0.005	—	—
MgCl ₂	—	—	0.01	0.0005	—
Glucose	[0.2]	[0.1-0.25]	0.1	0.05	0.1
Na ₂ HPO ₄	—	—	—	—	0.06
$\frac{M}{l}$ H ₃ PO ₄	—	—	—	—	0.02-0.06 c.c.

NEUTRALITY AND REACTION

Water is an invariable constituent of living protoplasm, of which it may form as much as 98 per cent. Most of the tissues in the human body contain about 80 per cent. of water. In every reaction taking place in the organism water plays an essential part. On dissociation the water molecule HOH forms oppositely charged hydrogen and hydroxyl ions. From a study of the conductivity of water purified to the highest possible extent, it is calculated that 1 litre at 22° C. contains 10^{-7} gramme ions of hydrogen, and of course the same amount of hydroxyl ions. The temperature coefficient of the electrolytic dissociation of water is fairly high, and at 18° C. is 5.32 per cent. for every degree, so that at 18° C. the hydrogen ion concentration in pure water is only 0.78×10^{-7} , while at 37° C. it is 1.76×10^{-7} .

Acidity is an expression of the concentration of hydrogen ions, while alkalinity is due to hydroxyl ions present. When these are equal in amount the reaction is said to be neutral. When a strong acid such as hydrochloric acid is added to a strong base such as NaOH, the hydrogen and OH ions combine to form molecules of water, so that the resulting solution contains only Na and Cl ions. The actual combination which takes place is thus the same whatever strong acid and strong base are used, namely, a combination of H and OH ions. On this account we find that the heat produced by the neutralisation of equivalent amounts of the most various acids is practically identical. In a solution containing H and OH ions, the active mass in any reaction which may take place is equal to the product of the two concentrations $H \times OH$. In a watery solution this is constant for any given temperature and amounts at 22° C. to 10^{-14} , increasing with the temperature; (at 37° it is 3.1×10^{-7}). Thus the more H ions are present in a solution the fewer will be the OH ions, and the change will occur very rapidly, since it is the product of the two and not the sum which remains constant.

The chemical reactions taking place in any solution in which H ions are concerned, or the behaviour of a living cell bathed by the solution, will be

determined, not by the total amount of alkali requisite to saturate the acid as in the ordinary methods of acidimetry, but by the actual concentration or

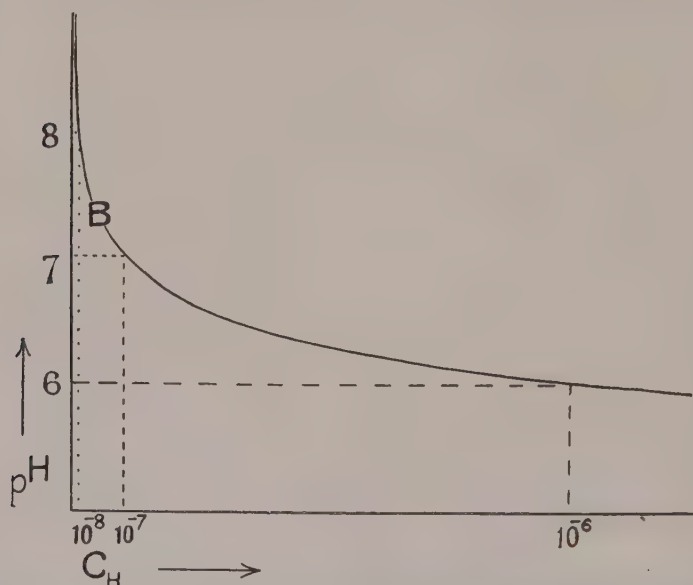


FIG. 19. Diagram to show the Relation between the two Methods of Registering Hydrogen Ion Concentration. (D. T. HARRIS.)

activity of the H ions in the solution at any given moment. It has therefore become of extreme importance to be able to express the reaction of the body fluids in terms of H ion concentration, denoted by cH , or of H ion activity caH .

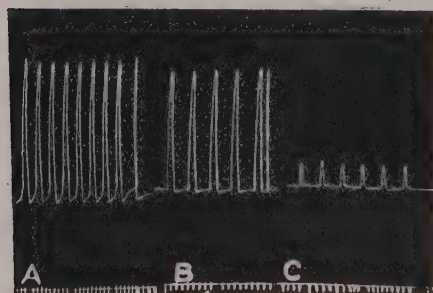


FIG. 20. Effect of Acid on the Isolated Heart of the Frog. (CLARK.)

- A. Perfused with Ringer's solution with H^+ ion concentration of $10^{-7.7}$.
- B. After perfusion for 20 minutes with faintly acid Ringer's solution, H^+ ion concentration, $10^{-6.5}$.
- C. After perfusion of the acid solution for 80 minutes.

Owing to the inconvenience of expressions such as 1.05×10^{-7} , 1.3×10^{-6} , &c., it has become customary to use, not the cH figure directly, but the negative exponent of 10 as a positive whole number, calling it the hydrogen ion exponent or pH. Thus 5×10^{-6} is the same as $10^{-5.3}$, and a solution having this concentration in H ions would be described as having a pH of 5.3. It must be remembered that the pH falls as the acidity increases. Moreover the change expressed by a unit difference in pH is much greater than that expressed by a unit difference in cH . Thus, while it is easy to see that the cH of 4×10^{-6} is double that of 2×10^{-6} , it is not at once obvious that a pH of 5.398 signifies an acidity which is double that of 5.699. The relation between the values of cH and of pH between $cH 10^{-8}$ and $cH 10^{-6}$ is shown in Fig. 19.

Since H and OH ions are involved in all the chemical processes which go on in the living cell, it is not surprising that the cell functions are profoundly modified by minute differences in reaction. In Fig. 20 is shown the effect

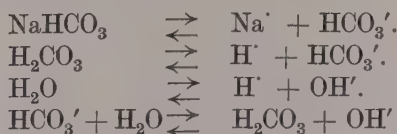
of a minute change in reaction, that is to say from alkalinity $10^{-7.7}$ to one of $10^{-6.5}$ on the isolated heart of the frog. This change would be produced by the addition of 0.036 milligrammes of HCl to 1 litre of distilled water. A slightly higher degree of acidity, *i.e.* one of 10^{-6} , would kill the heart altogether.

'BUFFER' SYSTEMS. In consequence of this sensitiveness of living protoplasm to minute changes in reaction, some means must be present in all organisms of minimising the changes of reaction which would be caused by production of minute quantities of acid or alkali in the various chemical processes continually taking place in the cell. This is effected by the presence of certain salts in the watery solution which forms the substratum of protoplasm as well as of the fluids of the body, in which the cells are bathed. These salts function as 'buffers' in taking up acid or alkali without a corresponding change in the reaction of the medium. The two principal are the bicarbonate system and the phosphate system, the former of chief importance in the fluids of the body, the latter in the cells.

The phosphate system is made up of the two phosphates NaH_2PO_4 and Na_2HPO_4 . In a watery solution of NaH_2PO_4 there are present, besides the H' and OH' ions from the water, Na' , $\text{H}_2\text{PO}_4'$, H' , and HPO_4'' ions from the phosphate. The H' ions are therefore present in greater quantity than in pure water, and the reaction is slightly acid. In a solution of Na_2HPO_4 , the ions resulting from dissociation of the phosphate are Na' , Na' , and HPO_4'' . The HPO_4'' ions combine with some of the H' ions derived from the water to form $\text{H}_2\text{PO}_4'$, leaving an excess of OH' ions, so that the reaction is slightly alkaline. Since it will require an equivalent weight of NaOH to convert 1 gramme molecule of NaH_2PO_4 into Na_2HPO_4 , and 1 gramme molecule of HCl to effect the reverse change, a mixture of the two phosphates will absorb relatively large quantities of acid or base with but slight changes in the resulting reaction.

The acidity (*i.e.* the hydrogen ion concentration) of a mixture of the two phosphates will be proportional to $\frac{\text{NaH}_2\text{PO}_4}{\text{Na}_2\text{HPO}_4}$. When this proportion equals $\frac{1}{2.5}$ the reaction will be neutral.

A still more perfect buffer system is afforded by NaHCO_3 , when the solution is maintained in equilibrium with an atmosphere containing a constant proportion of CO_2 . The solution will contain the following ions produced by dissociation.



H_2CO_3 is a very weak acid, so that only few hydrogen ions are produced. If an acid be added to the solution, a certain amount of the NaHCO_3 is decomposed with the formation of CO_2 and a neutral salt. But the CO_2 escapes from the solution, so that the only result is a diminished concentration of the NaHCO_3 .

The cH of the solution will be proportional to $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$, and the reaction will be neutral when $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3} = \frac{1}{3.75}$.

The salts of any weak acids (*e.g.* boric, lactic, &c.) may act as buffers,

ions. The E.M.F. actually observed is measured by comparing it with that of a standard (Weston) cell, as shown in the Figure, where R is a resistance, A an accumulator, EW a calibrated slide wire or potentiometer, W a Weston cell, and G a galvanometer. By means of the resistance R, the current through the potentiometer wire is balanced against the standard cell, so that there is a known fall of potential between the two ends of the wire, and no current flows through the galvanometer when the key T is closed. By means of the rider S_H a fraction of this potential is balanced against the E.M.F. of the hydrogen-calomel electrode battery until no current flows through the galvanometer on closing K. From the length of wire between P and the rider, we can read off at once the E.M.F. of the hydrogen-calomel battery, and thereby determine the hydrogen ion concentration in the fluid surrounding the hydrogen electrode.

The Glass Electrode. A method can be used which depends on the fact that a potential difference is set up between two solutions of different hydrogen ion concentrations, when these are separated by a very thin glass membrane. If the hydrogen ion concentration of one of the solutions is known, that of the other can be calculated from the difference of electrical potential. The method requires a special technique, but has certain advantages, one of which is that it is not necessary to de-oxygenate the solution.

Indicators. The hydrogen electrode method is not easy to apply in the case of physiological fluids, since in all of these part of the hydrogen ion concentration is due to the carbonic acid present in the solution. Bubbling of hydrogen through the fluid removes CO_2 and therefore alters the hydrogen ion concentration of the fluid. There are other factors which also interfere with the result, so that in most cases the estimation can be made more accurately and rapidly by means of *indicators*. These are certain dyes which change colour at definite values of hydrogen ion concentration. They are chiefly salts of either a very weak acid or a weak base, or the free acid or base itself, the change of colour being due to the electrolytic dissociation of the salt with the production of an ion which has a different colour from that of the undissociated acid or base. Some of the most useful indicators and the range of their concentrations are given in the following table. In determining the hydrogen ion concentration of fluids such as the blood, the reaction is tested in the dialysate obtained by placing the blood in a thimble of collodion, which is immersed in a small quantity of 0.85 p.c. NaCl solution (Dale and Evans method), care being taken to avoid loss of carbon dioxide. The dialysate acquires the same reaction as the blood, which is determined by adding a suitable indicator (neutral red or phenol red) and matching against standard buffer solutions to which the same indicator has been added.

COMMON INDICATORS FOR pH DETERMINATIONS.

Indicator.	Range, pH.	Acid Colour.	Alkaline Colour.
Methyl violet	0.1- 3.2	Yellow.	Violet.
Thymol blue (acid range)	1.2- 2.7	Red	Pale yellow.
Tetrabromphenol-sulphone-phthalein (bromphenol blue)	3.0- 4.6	Yellow.	Blue.
Methyl orange	3.2- 4.6	Red	Yellow.
Congo red.	3.5- 4.7	Blue	Red.
Methyl red	4.3- 6.3	Red	Yellow.
Neutral red	6.5- 8.4	Red (blue in strong acid solutions).	Yellow.
<i>p</i> -Nitro-phenol	5.0- 7.0	Colourless	Green-yellow.
Dibrom- <i>o</i> -cresol-sulphone-phthalein	5.2- 6.8	Yellow.	Purple.
Phenol red	6.8- 8.4	Yellow.	Red.
<i>o</i> -Cresol-sulphone-phthalein.	7.2- 8.8	Reddish	Orange.
α -Naphthol-phthalein.	7.6- 8.5	Yellow.	Blue.
Thymol blue (thymol sulphone-phthalein) (alkaline range)	8.0- 9.6	Pale yellow	Blue.
Phenol-phthalein	8.3-10.0	Colourless	Red.
Thymol-phthalein	9.3-10.5	Colourless	Blue.
Nitrothymolsulphonephthalein	9.2-11.5	Violet	Yellow.
Alizarin yellow	10.2-12.1	Yellow.	Orange.
Tropaeolin O	11.1-12.7	Yellow.	Orange.

SURFACE ENERGY

We have seen that protoplasm, the physical basis of the living cell, though fluid or semi-fluid, is not homogeneous. The fact that it consists largely of colloids involves a heterogeneity of structure : in fact, the alveolar appearance that may often be made out under the microscope may be taken as representing an ultra-microscopic structure, and as indicating a system composed of heterogeneous phases. The forces at the surface of a fluid differ in many respects from those in its interior. Within a liquid there is a strong attraction between its component molecules, producing an internal pressure. At the surface, any molecule, instead of being subject to the attraction of the other molecules on all sides, is exposed only to those attractions which tend to draw it inwards, so that as a result the surface is always the least possible and is pulling itself together, *i.e.* is in a state of tension. This surface tension can be measured in various ways, and is expressed in dynes per centimetre. To increase the surface requires the expenditure of energy, while work may be done if the surface is diminished. It is surface tension which causes water to rise in capillary tubes, and the height to which the water rises may be used as one means of measuring surface tension. If a fluid does not moisten the capillary tube, as in the case of mercury, there is a depression of the meniscus. Any substance which lowers the surface tension of water will tend to spread over its surface until it is one molecule thick. This is the case with oil dropped on water, the spreading of the oil being due to the contraction of the surface volume of water outside the part where its surface tension is diminished by contact with the drop of oil. Wherever we have two immiscible fluids there will be a surface tension, and in the same way there will be a surface tension between liquids and solids.

The surface tension of a liquid is altered by dissolved substances. Inorganic salts cause a slight rise of surface tension of a solution in contact with air. Most organic substances cause a diminution of surface tension. It was shown by Gibbs and Thomson that dissolved substances which lower surface tension tend to concentrate at the surface, on account of the fact that the free energy of the system is thereby lessened. In many cases this concentration at the surface may be so marked that the substance forms a solid pellicule. This is the case as we have seen (p. 22) with solutions of egg-white or of saponin.

When we are dealing with an interface between liquid and liquid or between liquid and solid, this concentration of solute or dissolved substance at the surface is equivalent to a deposition on the other substance with which the solution is in contact. The same factor is responsible for all cases of concentration at surfaces, for which the name *adsorption* is used. The marvellous power of absorption of gases by charcoal is due to the very large surface presented by this substance. In the dyeing of stuffs and the staining of sections adsorption is the chief factor involved. On chemically active solutes this process of adsorption will have a two-fold effect : that part which is adsorbed at the surface is taken out of the main solution and loses for instance its osmotic effect. On the other hand, the concentration of two reactive substances in the same surface may bring about their interaction, so that chemical changes are furthered which without this concentration would have gone on much more slowly. We shall have to deal with examples of this mode of action when we treat of enzymes.

Many surfaces are the seat of an electric charge. Most insoluble substances such as glass, paper, or wool, in water are negatively charged. This charge affects the adsorption which takes place on the surface of such

particles, and will tend to favour the concentration of electro-positive as against electro-negative molecules at the interface.

A charge on a surface implies a diminution of the surface tension. The change in surface tension under varying charge is made use of in the construction of the capillary electrometer, the surface tension increasing as the surface of the mercury is discharged and decreasing as its charge or polarisation is increased. Since electrolytes may augment or diminish the charge at a surface, we see the necessity for a proper adjustment of the constituents of a normal physiological solution to the properties of the surface of the living cells with which it has to come in contact.

THE FREE ENERGY OF CHEMICAL PROCESSES

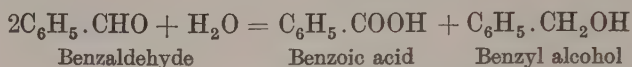
All the energies of the animal body are derived ultimately from the oxidation of foodstuffs, the actual processes of oxidation occurring by slow degrees in the cells of the body. For all practical purposes the heat of oxidation of one of the ordinary foodstuffs does not differ essentially from the free energy of that change. For the last thing that a living cell requires is heat. When the free energy of a cell is degenerated into heat energy, it is wasted. We know that in our machines only a small proportion of heat energy can be utilised for work, and in an isothermal system none at all. Within the minute space of a cell there is no possibility of any significant differences of temperature: the whole cell cools or warms together. It is only quite late in evolution that a use was found for the waste heat of the chemical processes of the cell, viz. in raising the temperature of the whole animal, so as to quicken all its powers of reaction and adaptation, and in maintaining its temperature at a constant level, so that its rapidity of response should be independent of the temperature of the environment.

But the life of a cell or of an animal, composed of myriads of these minute isothermal units, involves movement, repair, growth, secretion of definite chemical substances, excretion against osmotic forces, transmission of impulses and the whole mechanism of correlation for the production of appropriate reactions—all processes which mean external or internal work. For these purposes free energy is required, and this must be derived from chemical changes occurring in the living cell independently of the production of heat. In any isothermal change the free energy is the maximum external work which could be done under the best imaginable conditions; the free energy of a change is independent of the path of change, as is the total energy—the heat production; the free energy may, in general, be greater than, equal to, or less than, the heat production. It involves a system, *i.e.* it is organised energy, whereas heat is unorganised energy, only convertible into work under special conditions and then to a degree limited by these conditions.

In the circumstances existing in the living cell, *i.e.* an isothermal system set in an isothermal medium infinite in relation to the cell, every reaction or change in the system will tend to diminish the free energy, the loss being equal to the maximum external work which the system could have produced in the change. As a matter of fact, the system is never perfect, nor is the maximum work attained, the difference appearing as heat and being wasted, except when it can be utilised for maintaining a stable body temperature, at a level above that of the surrounding medium.

It is important to note that the second law of thermodynamics, which affirms the diminution of free energy in any isothermal change, applies to the whole (supposed isolated) system, even when this is a cell of microscopic

dimensions, and not to any individual constituent of the system. Thus we find that in the body there may be changes which raise the chemical potential of a substance, *i.e.* convert it into another body having more potential energy, provided the reaction is coupled with one involving a diminution of potential. Thus the oxidation of benzaldehyde is often accompanied with a simultaneous reduction, so that both benzoic acid and benzyl alcohol are formed :



It is probable that the recovery process in muscle, where a small fraction of the lactic acid formed in the previous contraction is oxidised with the production of heat, while the greater part of the lactic acid is reconverted into glycogen, belongs to this class of coupled reactions ; and we shall meet other examples in dealing with the processes of oxidation in the body.

THE ENERGETIC BASIS OF THE BODY

CHAPTER VII

THE PROPERTIES OF COLLOIDS

ALTHOUGH the chemical changes involved in the various vital phenomena occur between substances in watery solution, the solution in every case is bound up within the meshes or adsorbed by the surfaces of a heterogeneous mass of colloids. The complex molecules which make up protoplasm itself are all colloidal. The participation of colloids in chemical reactions introduces conditions and modes of reactions differing widely from those in watery solutions. Our knowledge of these conditions is still very imperfect, but the important part played by colloids in the processes of life renders it necessary to discuss their properties in some detail.

The term colloid, from κόλλη, glue, was first introduced in 1861 by Thomas Graham, Professor of Chemistry at University College. Graham divided all substances into two classes, viz. crystalloids, including such substances as salt, sugar, urea, which could be crystallised with ease, diffused rapidly through water and were capable of diffusing through animal membranes; and colloids, which included substances such as gelatin or glue, gum, egg-albumen, starch and dextrin, were non-crystallisable, formed gummy masses when their solutions were evaporated to dryness, diffused with extreme slowness through water and would not pass through animal membranes. The process of dialysis was therefore introduced by Graham for the separation of crystalloids from colloids. Although the broad distinction drawn by Graham between colloids and crystalloids still holds good, some of the criteria by which he distinguished the two classes are no longer strictly applicable. For instance it has been shown that many typical colloidal substances, such as hæmoglobin, can be obtained in a crystalline form. On the other hand all gradations exist between substances, such as egg-albumen, which are practically indiffusible, and those, such as common salt, which are very diffusible. Graham pointed out that colloids exist under two conditions:

(1) In a state of solution or pseudo-solution, in which they form *sols*, and are distinguished as hydrosols when the solvent is water; and

(2) In a solid state, in which a relatively small amount of the colloid sets with a large amount of a fluid, such as water, to form a jelly. This solid form is known as a *gel*. The most familiar instance is the jelly which is obtained on dissolving a little gelatin in hot water and allowing the mixture to cool. Such a jelly is known as a *hydrogel*.

A number of these colloidal substances can be shown on purely chemical grounds to consist of monstrous molecules. Thus the molecular weight of hæmoglobin is at least 16,000, and one must ascribe similar high molecular weights to such substances as egg-albumen and globulin. Still greater must be the molecular size of such substances as the cell proteins, which may

be made up of more than one type of protein built up with various nucleins, with lecithin and cholesterol, to form a gigantic complex, to which it would probably not be an exaggeration to ascribe a molecular weight of over 100,000. This chemical complexity is not however a necessary condition of the colloidal state, as is shown by the existence of colloidal silica, of colloidal ferric hydrate and alumina, and even of colloidal elements.

On neutralising a weak solution of sodium silicate or water-glass by means of HCl, we obtain a solution which contains sodium chloride and silicic acid. On dialysing this mixture for some days against distilled water, the whole of the NaCl passes out, and a solution of silicic acid or colloidal silica is left in the dialyser. This solution can be concentrated over sulphuric acid. When concentrated to a syrupy consistence it becomes extremely unstable. The addition of a minute trace of sodium chloride or other electrolyte to the solution causes it to set at once to a solid jelly (gelatinous silica), the change being accompanied by an appreciable rise of temperature. The change is irreversible, in that it is not possible to bring the silicic acid into solution again by removal of the electrolyte by means of dialysis. If however it be allowed to stand with weak alkali for some time, it gradually passes into solution. Analogous methods are employed for the preparation of colloidal Fe_2O_3 and Al_2O_3 .

All so-called colloidal solutions are in reality suspensions. Of special interest are the colloidal solutions of the metals. Faraday long ago pointed out that, on treating a weak solution of gold chloride with phosphorus, it underwent reduction with the formation of metallic gold. The gold was not precipitated, but remained in suspension or pseudo-solution, giving a deep red * or a blue liquid, according to the conditions under which the reaction was effected. This solution was homogeneous in that it could be filtered without change and could be kept for months without deposition of the gold. The latter was however thrown down on addition of mere traces of impurity, though greater stability could be conferred on the solution by adding to it a little 'jelly,' e.g., a weak solution of gelatin. In 1899 Bredig showed how similar hydrosols might be prepared from a number of different metals, viz. by the passage of a small arc or electric sparks between metallic terminals submerged in distilled water. If for example the terminals be of platinum, the passage of the current is seen to be accompanied by the giving off of brown clouds, which spread into the surrounding fluid. These clouds consist of particles of platinum of all sizes. The larger settle at the bottom of the vessel, the smaller—which are ultra-microscopic in size, i.e. from $5\ \mu\mu$ to $40\ \mu\mu$ †—remain in suspension, and we obtain a brown fluid which can be filtered through paper or even through a Berkefeld filter without losing its colour. It may be kept for months without any deposit taking place. The addition of minute traces of electrolytes precipitates the platinum particles, leaving a colourless fluid. We shall have to return later on to the consideration of the behaviour of these metallic sols.

Colloidal solutions or sols may be divided into two classes, *emulsoids* and *suspensoids*, according as they may be regarded as suspensions of liquid or as suspensions of solid particles in liquid.

Most protein solutions are emulsoids, while the metallic sols belong to the class of suspensoids. Dilute egg-white is an emulsoid, but if it be boiled, although no visible precipitation is produced, the fine particles are coagulated and it behaves as a suspensoid.

PROPERTIES OF GELS. The firm mass to which a solution of gelatin sets on cooling is a typical hydrogel. It is clear, hyaline, apparently

* Ruby glass is a colloidal 'solid' solution of gold in a mixture of silicates.

† One μ is one-thousandth of a millimetre; one $\mu\mu$ is one-thousandth μ , i.e. one-millionth of a millimetre.

structureless and possesses considerable elasticity, *i.e.* resistance to deforming force. It may be regarded as formed by the separation of the warm pseudo-solution of gelatin into two phases: first a solid phase, rich in gelatin and forming a tissue or meshwork in the interstices of which is embedded the second phase, consisting of a very weak solution of gelatin.

If the process be observed under the microscope, according to Hardy minute drops first appear which, as they enlarge, touch one another and form networks. In a stronger solution the first structures to make their appearance consist, not of the more concentrated phase but of droplets of the dilute solution of gelatin; the stronger solution collects round these drops and solidifies to a honeycomb structure.

In many cases the more fluid part of the gel is practically pure water. In a dry atmosphere the gel loses water and becomes shrivelled and dry, but in some cases, *e.g.* gelatin, it can resume its former size and characters on immersion in water. Other gels, such as silicic acid or ferric hydrate, lose the power of swelling up after drying. The change in them is therefore irreversible. A gel adheres to the last traces of water with extreme tenacity. In consequence of its structure, it presents an enormous extent of surface on which adsorption can take place. At this surface the vapour tension of fluids is diminished as well as the osmotic pressure of dissolved substances. On this account gelatin must be heated for many hours at a temperature of 120° C. in order to be thoroughly dried. When dry, colloids can exert a considerable amount of energy when caused to swell up by moistening. This energy was made use of by the ancient Egyptians in the quarrying of their stone blocks by the insertion of wedges of wood; water was poured on the wood and the swelling of the wedges split the rock in the desired direction.*

On account of the extent of surface it is practically impossible to wash out the inorganic constituents from a gel. The diminution of the osmotic pressure of many dissolved substances at surfaces causes the concentration at the surface of the solid phase to be greater than that in the surrounding medium. Thus if dry gelatin be immersed in a salt solution it will swell up, but the solution which it absorbs will be more concentrated than the solution in which it is immersed, so that the proportion of salt in the latter will be diminished. When however equilibrium is established between a gel and the surrounding fluid, it is found to present no appreciable resistance to the passage of dissolved crystalloids. Thus salt or sugar diffuses through a column of solid gelatin as if the latter were pure water. On the other hand gels are practically impermeable to other colloids in solution. This impermeability is made use of in the separation of crystalloids from colloids by dialysis, membranes used in this process being generally irreversible and heterogeneous gels (*i.e.* vegetable parchment, animal membranes, collodion or cellophane). Other gels, such as tannate of gelatin or copper ferrocyanide, are not only impermeable to colloids, but also to many crystalloid substances. These membranes can therefore be used for the determination of the osmotic pressure of crystalloids.

PROPERTIES OF HYDROSOLS. Substances such as dextrin or egg-albumin may be dissolved in water in almost any concentration. If a solution of egg-albumin be concentrated at a low temperature, it becomes more and more viscous and finally solid. But there is no distinct point at which the fluid passes into the solid condition. Such solutions are known as hydrosols. Much discussion has arisen whether they are to be regarded as true solutions or as pseudo-solutions or suspensions. The chief criterion

* According to Rodewald, the maximal pressure with which dry starch attracts water amounts to 2073 kilo. per sq. cm.

of a true solution is its homogeneity. In a solution the molecules of the solute are equally diffused throughout the molecules of the solvent, and it is impossible, without the application of energy, to separate one from the other. Thus filtration or gravitation leaves the composition of the solution unchanged. It is true that by the employment of certain kinds of membranes, *e.g.* the semi-permeable copper ferrocyanide membrane, it is possible to separate solute from solvent, but in this case the force required to effect the filtration is enormous and grows with every increase in the strength of the solution. The measure of the force required is the osmotic pressure of the solution, and it becomes natural therefore to regard the possession of an osmotic pressure as a distinguishing criterion of a true solution. Is there any evidence that colloidal solutions also display an osmotic pressure?

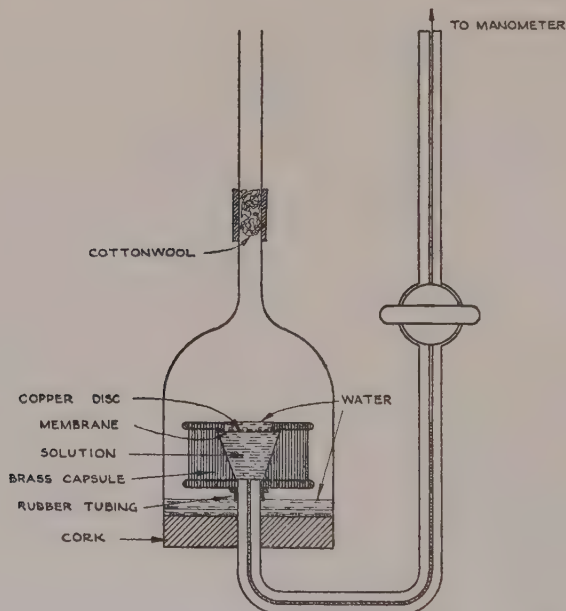


FIG. 22. Govaerts' Osmometer (Verney's modification). (KERRIDGE.)

I have shown that it is possible to determine the osmotic pressure of colloidal solutions directly, taking advantage of the fact that colloidal membranes, while permitting the passage of water and salts, are impermeable to colloids in solution.

In this way it was found that blood serum containing 7 to 8 per cent. of proteins had an osmotic pressure of 25 to 30 mm. Hg, which would correspond to a molecular weight of the protein, of about 30,000.

A convenient osmometer for this purpose is that of Govaerts, and illustrated in Fig. 22. The membrane is of cellophane, supported by a perforated copper disc. The serum or other solution is placed in the brass capsule, and water on the upper surface of the membrane. The level of serum in the glass capillary is kept constant by applying counter-pressure from a manometer, to balance the osmotic pressure, and this counter pressure is read off when equilibrium is reached. The osmometer is kept at a suitable temperature in a water bath. Instead of cellophane, parchment paper may be used.

With the osmometer, the existence of an osmotic pressure in colloidal solutions has been definitely established both by Moore in the case of hæmoglobin, proteins and soaps, and by Bayliss in the case of colloidal dyes such as Congo red. The osmotic pressure of

hæmoglobin has been found by Adair to correspond to a molecular weight of about 66,000, *i.e.* about 4 times as great as the minimal molecular weight deduced from its composition and its combining powers with oxygen. The osmotic pressure is often very much smaller than would be expected from the molecular weight of the substance, owing to the fact that colloids in solution may be in many different conditions of aggregation. Thus the aggregate of colloidal silica must be many, probably thousands of, times larger than the molecule as represented by H_2SiO_3 . The osmotic pressure being proportional to the number of separate molecules or groups of molecules in a given volume of solution, the larger the aggregate the smaller would be the total number of groups, and the smaller therefore the osmotic pressure of the solution.

It is in consequence of the huge size of the molecular aggregates that colloidal solutions, such as starch or glycogen and probably globulin, display no appreciable osmotic pressure. We cannot divide colloidal solutions into two classes, *viz.* those which form true solutions and present a feeble osmotic pressure, and those which form only suspensions and therefore exert no osmotic pressure. In inorganic colloids, such as arsenious sulphide, Picton and Linder have shown that all grades exist between true solutions and suspensions. With increasing aggregation of the molecules, the suspension becomes coarser and coarser until finally the sulphide separates in the form of a precipitate.

We have every reason to believe that the very complex molecules forming the cell proteins may have molecular weights even greater than 30,000. When however we arrive at molecular weights of these dimensions, the disproportion between the size of the molecules and those of the solvent, water, becomes so great that a homogeneous distribution of the two substances, solute and solvent, is no longer possible. The size of a molecule of water has been reckoned to be 0.7×10^{-8} mm. A molecule 10,000 times as large would have a diameter of 0.7×10^{-4} mm. = 0.07μ , a size just within the limits of microscopic vision. Long before molecules attained such a size they would no longer react according to the laws of solutes which have been derived from the study of the behaviour of the almost perfect gases, but would possess the properties of matter in mass. They have a surface of measurable extent, and their relations to the molecules of water or solvent will be determined by the laws of adsorption at surfaces rather than by the laws of interaction of molecules. As a matter of fact we find that such solutions present an amazing mixture of properties, some of which betray them as mechanical suspensions, while others partake of the nature of the chemical reactions such as those studied in the simpler compounds usually dealt with by the chemist.

OPTICAL BEHAVIOUR OF HYDROSOLS. Nearly all colloidal solutions present what is known as the Faraday-Tyndall phenomenon. When a beam of light is passed through an optically homogeneous fluid, the course of the beam is invisible. A beam of sunlight falling into a dark room is rendered visible by impinging on and illuminating the dust particles in its course. Each of these particles, being illuminated, acts as a centre of dispersion of the light, so that the course of the beam is apparent to a person standing on one side of it. Tyndall showed that, if the particles were sufficiently minute, the light dispersed by them at right angles to the beam was polarised. This can be easily tested by looking at the beam through a Nicol's prism. If the prism be slowly rotated, it will be found that, while at one position the light is bright, in the position at right angles to this it becomes dim or is extinguished. The Tyndall phenomenon may therefore be regarded as a test for the presence of ultra-microscopic particles, varying in size from 5 to 50μ . The phenomenon is perhaps too sensitive to be taken as a proof that a fluid presenting it is a suspension rather than

a solution. It is shown for instance by solutions of many bodies of high molecular weight, such as raffinose (a tri-saccharide) or the alkaloid brucine (Bayliss).

A particle having a diameter less than half the wave-length of light, *i.e.* about 300λ or 0.3μ , cannot be clearly distinguished under any power of the microscope. The fact that an ultra-microscopic particle may serve as a centre for dispersal of light may be used for rendering the position of such particles visible under the microscope. For this purpose a strong beam of light is passed in the plane of the stage of the microscope through a cell containing the hydrosol, which is then examined under a high power. On examining a dilute gold sol with this apparatus, we see a swarm of dancing points of light, "like gnats in the sunlight," which move rapidly in all directions, rendering it almost impossible to count their number in the field. The coarser particles present slight oscillations similar to those long known as the Brownian movements. The smallest demonstrable particles show a combined movement, consisting of a translatory movement, in which the

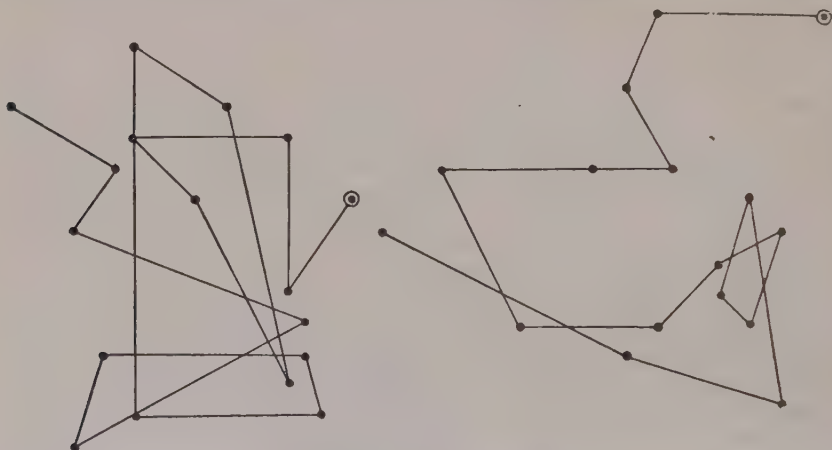


FIG. 23. Movements of two Particles of India-rubber Latex in Colloidal Solution, recorded by cinematograph and ultra-microscope. (HENRI.)

particle passes rapidly across the field in one-sixth to one-eighth of a second, with one of oscillation of much shorter period. The representation of the course of such a particle is given in Fig. 23.

The size of the smallest particles revealed in this way may amount to 0.005μ . Not all colloidal solutions show these particles in the ultra-microscope. In some cases this is due simply to the small size of the particles, and the addition of any substance, which causes aggregation and therefore increase in the size of the particles, will bring them into view. In others the absence of optical inhomogeneity may be due to the coincidence of the refractive indices of the two phases of the hydrosol, or to the absence of any surface tension and therefore dividing surfaces between the two phases. In any case it must be clearly understood that it is not the particle itself which is thus rendered visible, but only the light scattered from it.

ELECTRICAL PROPERTIES OF COLLOIDS

In the case of many hydrosols the ultra-microscopic particles of which they are composed carry an electric charge which, according to the nature of the solution, may be either positive or negative. On this account

the particles move if placed in an electric field, and the direction of their movement reveals the nature of their charge. Thus colloidal ferric hydrate is electro-positive and travels to the cathode. Silicic acid, in the presence of a trace of alkali, is electro-negative, and the same is true of a hydrosol of gold. When a current is passed through these hydrosols, the colloidal particles travel to the anode where they are precipitated. In certain colloids the charge varies according to the conditions under which they are brought into solution. If for instance egg-white be diluted ten times with distilled water, filtered and boiled, no precipitate occurs but we obtain a colloidal suspension of albumin. When thoroughly dialysed, this protein is insoluble in pure water but is soluble in traces of either acid or alkali. In acid solution the protein particles carry a positive charge, whereas in alkaline solution their charge is negative. The charged condition of these particles must play a considerable part in keeping them asunder and therefore in preventing their aggregation and precipitation. This is shown by the fact that any agency which will tend to discharge them will cause precipitation and coagulation. Among such agencies is the passage of a constant current, just mentioned. To the same action are due the coagulative or precipitating effects of neutral salts. Thus any of the colloids we have mentioned, ferric hydrate, silica, gold or boiled albumin, are thrown down by the addition of traces of neutral salts, and it is found that in this process they carry with them some of the ion with the opposite charge to that of the colloidal particle. Thus in the precipitation of the electro-positive ferric hydrate, the acid ion of the salt is the determining factor, the coagulative power increasing rapidly with the valency of the acid. On the other hand in the precipitation of a gold sol, the electro-positive ion is the effective agent, and here again the coagulative effect is enormously increased by a rise in valency. This is shown in the following Table, where it will be seen that in the coagulation of gold, barium chloride with the divalent Ba^{++} is 7 times as powerful as K_2SO_4 containing the univalent K^+ ; whereas, in the precipitation of the electro-positive ferric hydrate, K_2SO_4 with a divalent SO_4^{--} is 400 times as effective as BaCl_2 .

AMOUNT OF SALT NECESSARY TO PRECIPITATE COLLOIDAL SOLUTIONS

To coagulate Gold		To coagulate Fe_2O_3	
K_2SO_4	1 g. mol. in 4,000,000 c.c.	BaCl_2	1 g. mol. in 500,000 c.c.
MgSO_4	" " " 4,000,000 "	NaCl	" " " 72,000 "
BaCl_2	" " " 10,000 "	K_2SO_4	" " " 75,000 "
NaCl	" " " 30,000 "		

The presence of a charge is not however a necessary condition for the stability of a colloidal solution. Thus the proteins of serum globulin in a neutral saline solution, or gelatin, present no drift when exposed to a strong electric field. In such cases one must assume the stability of the solution to be determined by the absence of any surface tension between the two phases in the solution, or between the particles of solute and solvent. Thus no force is present tending to cause aggregation of the particles.

The charged condition of a colloidal particle makes it behave in an electric field in much the same way as a charged ion of an electrolyte, and this similarity extends also to its chemical behaviour, so that we can have a class of combinations formed resembling in many respects chemical compounds, but differing from them in the absence of definite quantitative relations between the reacting substances. This class of continuously varying compounds has been designated adsorption compounds or complexes.

The factors involved in the formation of adsorption combinations are therefore :

(1) Extent of surface. In a colloidal solution this is enormous in proportion to the mass of substance in solution. Thus a 10 c.c. sphere with a surface of 22 sq. cm., if reduced to a fine powder consisting of spherules of $2.5 \mu\mu$ in diameter, will have a surface of 20,000,000 sq. cm., *i.e.* nearly half an acre. At the whole of this surface adsorption may take place, involving the concentration of dissolved electrolytes, ions or gases.

(2) Chemical nature of particle.

(3) Electric charge on the surface. The sign of this may be determined by the chemical nature of the colloid and its relation to the electrolytes in the surrounding medium.

Another factor which may determine the character of the charge on the particles has been pointed out by Coehn. This observer finds that, when various non-conducting bodies are immersed in fluids of different dielectric constants, they assume a positive or negative charge according as their own dielectric constants are higher or lower than the fluid with which they are in contact. For instance, glass (5 to 6) is negative in water (80) or alcohol (26), whereas in turpentine (2.2) it is positive. In water, as Quincke has found, nearly all non-conducting bodies take on a negative charge. Among these are cotton-wool and silk. Particles of these in water, exposed to an electric field, move towards the anode. The same is true, as Bayliss has shown, of paper.

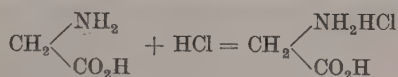
The conditions which determine the formation of these adsorption compounds can be studied in their simplest form on the adsorption of dyestuffs by substances such as paper. If we take a series of solutions of a dye, such as Congo red, in progressively diminishing concentration, and place in each solution the same amount of filter-paper, we find that a part of the dye is taken up by the paper, and the proportion taken up is larger the more dilute the solution. This relation has been spoken of by Bayliss as the *law of adsorption*. This is illustrated by the following Table of results of such an experiment :

Concentration of Solution.		Proportion of Dye in Solution.	Proportion of Dye in Paper.
Initial.	Final.	Per cent.	Per cent.
0.014	0.0056	40	60
0.012	0.0024	20	80
0.010	0.0009	9.3	90.7
0.008	0.0003	4	96
0.006	0.00008	1.3	98.7
0.004	—	trace	practically all
0.002	—	trace	practically all

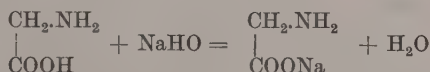
If put into the form of a curve, where the ordinates represent the percentage of dye left in solution and the abscissæ the original concentration of the solution, the curve only approaches the axis (*i.e.* zero concentration) asymptotically. In other words, however dilute the original solution may be, there will always be a certain amount of the dye left unabsorbed by the paper. Similar relations are found to exist between proteins and electrolytes. By continuously washing a protein, *e.g.* gelatin with distilled water, the removal of electrolytes becomes slower and slower, but it is practically impossible within finite time to get rid in this way of the last traces of ash.

Although the chemical behaviour of colloids is largely determined by surface phenomena, it presents at the same time analogies with more strictly chemical reactions, since it is conditioned by the chemical structure of the colloid molecule as well as by the charge carried by the latter. A good

example of these adsorption combinations is presented by globulin, the behaviour of which has been studied by Hardy. Four states can be recognised in both the solid condition and in solution, viz. globulin itself, compounds with acid or with alkali, and compounds with neutral salt. The amount of acid and alkali combining with the globulin is indeterminate, the effect of adding either acid or alkali to the neutral globulin being to cause a gradual conversion of an opaque, milky suspension into a limpid, transparent solution. On drying HCl globulin, the dried solid is found to contain all the chlorine used to dissolve it. The acid may therefore be regarded as being in true combination. Both acid and alkali globulins act as electrolytes, the globulin being electrically charged and taking part in the transport of electricity. In order to produce the same degree of solution, the concentration of the alkali added must be double that of the acid. The relation of globulin to acids and alkalies is similar to that of the so-called *ampholytes* or amphoteric substances, such as the amino-acids. An amino-acid such as glycine can react as a basic anhydride with other acids thus :



or as an acid with bases :



Like these too, globulin forms soluble compounds with neutral salts. An amphoteric electrolyte thus acts as a base in the presence of a strong acid and as an acid in the presence of a strong base.

From true electrolytes, colloidal solutions differ in the fact that their particles are of varying size according to the conditions in which they exist and carry varying charges of electricity, whereas an ion such as Na⁺ or Cl⁻ has a mass which is constant for the ion in question and always carries the same electric charge. The charged particles of an acid- or alkali-globulin may be distinguished therefore as *colloidal* or *pseudo-ions*. Whether a protein has a positive or a negative charge depends chiefly on the hydrogen ion concentration of the medium. At a certain H-ion concentration, known as the *isoelectric point*, it carries no charge and it then exhibits maximum precipitability (it often flocculates out), minimum viscosity, minimum osmotic pressure, and minimum imbibition.

In these adsorption combinations, although the chemical nature of the colloidal molecules is concerned, there is an absence of definite equilibrium points such as we are accustomed to in most chemical reactions. The inertia of the system and the large size of the molecules determine the occurrence of false equilibria and of delayed reaction, so that the condition and behaviour of a colloidal system at any moment are determined, not entirely by the quantitative relations of its components but also by the past history of the system.

COMBINATIONS BETWEEN COLLOIDS. Besides the compounds between colloids and electrolytes, combination or at least interaction takes place between different colloids. Many colloids are precipitated by other colloidal solutions. This effect is always found to occur when the colloidal solutions carry different charges. Thus ferric hydrate in colloidal solution is precipitated by colloidal silica or colloidal gold, both colloids being thrown out of solution. On the other hand certain colloids may exercise a protective influence on other colloidal solutions. Thus, as Faraday first showed, colloidal

gold is much more stable in the presence of a little gelatin. The colloids of serum can dissolve a considerable amount of purified globulin. Although the latter in solution shows a drift in the electric field, the resulting solution is quite unaffected by the passage of a current through it. In these cases the protective colloids carry no charge, but the same protective effect may be observed if a large excess of *e.g.* an electro-positive colloid be added to an electro-negative colloid. This interaction between different colloids probably plays an important part in many physiological phenomena. We have reason to believe that the reactions between toxin and antitoxin and between enzyme and substrate, which we shall study later, are of this character, and that the compounds formed belong to the class of adsorption combinations.

THE COAGULATION OF COLLOIDS

Most colloidal solutions are unstable, and the relations between the suspended particle or molecule and the surrounding fluid may be upset by slight changes of reaction or the presence of minute traces of salts. As a result the hydrosol is destroyed, the suspended particles aggregating to form larger complexes. These aggregations may settle to the bottom of the fluid as a precipitate or may form a species of network, the result varying according to the nature of the colloid and its concentration. Thus gelatin changes from the condition of hydrosol to hydrogel with fall of temperature. The same is true of agar. On the other hand, by adding calcium chloride to an alkaline solution of casein, we obtain a mixture which sets to a jelly on warming but becomes fluid again on cooling. Other agencies may lead to the production of changes which are irreversible. Thus a strong solution of colloidal silica sets to a solid jelly on the addition of a trace of neutral salt, and it is not possible to reform the hydrosol, however long the jelly is submitted to dialysis.

The huge molecules or aggregates of molecules, which distinguish the colloidal state, form a system with a considerable inertia, so that there is a tendency to the establishment of conditions of false equilibrium. Once a configuration is established, it is necessary, in consequence of the inertia, to overstep widely the conditions of its formation in order to destroy it. Thus a 10 per cent. gelatin solution sets at 21° C. but does not melt until warmed to 29.6° C. Solutions of agar in water set at about 35° C. but do not melt under 90° C. A gel of gelatin takes twenty-four hours after setting to attain a constant melting point. This phenomenon is called *hysteresis*.

Two methods of bringing about coagulation of hydrosols deserve special mention. The first of these is heat coagulation. If a solution of egg-albumin or globulin be heated in neutral or slightly acid medium and in the presence of neutral salt, the whole of it is thrown down in an insoluble form. This coagulated protein is insoluble in dilute acids or alkalies. The same coagulative effect of heating is observed in the metallic sols. With concentrated solutions of protein, heat coagulation results in the formation of a gel, *i.e.* a network of insoluble protein, containing water or a very dilute solution of protein in its meshes. In dilute solutions the result is the production of a flocculent precipitate.

Another method is the so-called mechanical coagulation. If a solution of globulin or albumin be violently shaken, a shreddy precipitate makes its appearance in the solution, and by prolonged shaking it is possible to throw down 80 or 90 per cent. of the dissolved protein in the coagulated form. Ramsden has shown that this mechanical coagulation is a surface phenomenon. It depends on the fact that substances in solution which lower the

surface tension undergo concentration at the free surface of the fluid. Such substances are proteins, bile salts, quinine, saponin, &c. In the case of proteins the concentration reaches such an extent, and the molecules at the surface are so closely packed together that they form an actual solid pellicle. When the solution is violently shaken, new surfaces are constantly being formed, and as the older surfaces are withdrawn into the fluid, the solid pellicle on them is rolled up into a fine shred of coagulated protein.

The distinguishing features of a colloidal solution are due to the fact that in every solution there are two phases—a fluid or *continuous* phase, and a second disperse phase which is either solid or a concentrated or super-saturated solution of the colloid. The huge size of the molecules and the development of surface not only determine the formation of adsorption combinations but, on account of the inertia of the system, cause a delay in changes of state and tend to the formation of false equilibria dependent on the past history of the system.

IMBIBITION

All colloids, even those such as starch or gelatin which are insoluble in cold water, exhibit a phenomenon, viz. '*Quellung*' or imbibition, which in many cases it is impossible to distinguish from the process of solution. This phenomenon, which was long ago studied by Chevreul and has been the subject of a series of careful experiments by Overton, is exhibited by all animal tissues and all colloids. Thus elastic tissue dried *in vacuo* absorbs from a saturated solution of common salt 36·8 per cent. of water and salt. If dried colloids be suspended in a closed vessel over various solutions, they will take up water in the form of vapour from the solution, and the osmotic pressure of the solution in question will inform us as to the amount of work which would be necessary in order to separate the water again from the colloids.

Thus it has been reckoned that to press out water from gelatin containing 28·4 parts of water to 100 parts of dried gelatin would require a pressure of over 200 atmospheres. The imbibition pressure of colloids increases rapidly with the concentration of the colloid and at a greater rate than the latter. In this respect however imbibition pressure resembles osmotic or indeed gaseous pressure. It is impossible to draw any hard line of distinction between imbibition pressure and osmotic pressure, or to say where a fluid ceases to be a solution and becomes a suspension.

The close connection between the processes of imbibition and of solution is shown also by the fact that the latter occurs only in certain media, the nature of the media being dependent on the chemical character of the substances in question. Thus all the crystalline carbohydrates—such as grape sugar and cane sugar—are easily soluble in water, only slightly soluble in alcohol, and practically insoluble in ether and benzene. The amorphous carbohydrates, which must be regarded as derived by a process of condensation from the crystalline carbohydrates—e.g. starch, cellulose, gum arabic, &c.—have a strong power of imbibition for water. This power may be limited as in the case of cellulose, or may be unlimited as in the case of gum arabic so that a so-called solution results. On the other hand they swell up but slightly in alcohol and are unaffected by ether and benzene. In the same way proteins all take up water and in many cases form a so-called solution, but are unaffected by ether and benzene—a behaviour which is repeated in the case of the amino-acids, out of which the proteins are built up. India-rubber, however, and the various resins take up ether, benzene and turpentine often to an indefinite extent, while they are untouched by water. With this behaviour we may compare the easy solubility of the hydrocarbons, the aromatic acids and esters in ether and benzene, and their insolubility in water. As Overton has pointed out, the power of amorphous carbohydrates to take up fluids is modified by alteration of their chemical structure in the same direction as the solubility of the corresponding crystalline carbohydrates. Thus if the hydroxyl groups in the carbohydrates be replaced by nitro, acetyl or benzoyl groups, they become less soluble in water, while their solubility in alcohol, acetone, &c., is increased.

THE ENERGETIC BASIS OF THE BODY

CHAPTER VIII

THE PASSAGE OF WATER AND SALTS ACROSS MEMBRANES

THE heterogeneous structure of the body involves the presence of surfaces of separation, which may be of any order of size, molecular, microscopic, or evident on simple dissection. In the single cell the membrane bounding the cell and separating it from its environment is as a rule invisible under the microscope and of molecular dimensions: such is the Plasma membrane (described in Chapter II.) which is essential for the retention of the individuality of the cell. Similar membranes of molecular dimensions must be assumed to be present round the contractile vacuoles in the *amœba*, bounding the cell nucleus, and determining the histological differentiation, such as may be observed in a living muscle cell and in the constituent parts of the nucleus. In other cases the membrane is of a definite thickness: it may be apparently structureless and homogeneous such as the elastic lamina in the back part of the cornea of the eye, or it may be made up of cells of various shapes. The bounding membrane of the blood capillaries is composed of flat cells, and the lining membrane of the lung alveoli is similarly composed of very thin flat cells; or the membrane may consist of cubical or columnar cells, as in those forming the lining membrane of the small intestine or the essential part of secreting glands. In such a cellular or compound membrane any transference across the membrane may be regulated by the cells themselves, each of which may act as a pump, taking up a substance on one side and turning it out on the other, in many cases after having undergone modification under the influence of the metabolic processes of the cell. It is impossible however to investigate the part played by these cells in the transference of substances across a membrane unless we know what factors determine the passage of water and dissolved substances across membranes which do not take an active part in the process of transference, and in which all the energy must be derived from the forces present in the fluids and dissolved substances undergoing transference. We shall consider in this chapter the conditions which determine such a transference across a membrane. Such a membrane we can imagine of any thickness, from one molecule upwards, since the thickness will affect only the rate of passage of substances across it. Surface films, one molecule in thickness, are readily formed on liquids, *e.g.* when fatty acids are placed on water. In such a case the molecules are arranged vertically, with the carboxyl groups next the water. Similar *mono-molecular films* are also in all probability formed at the surface of colloid solutions and, as a general case, at surfaces where adsorption occurs.

The following forces may be concerned in causing the movement of water or dissolved substances across a membrane :—

(1) **HYDROSTATIC PRESSURE.** The significance of this is familiar in the ordinary process of filtration. In order to quicken the rate of filtration it is usual to employ a filter pump, which merely increases the difference of pressure between the two sides of the filtering membrane. The denser the membrane the greater will be the difference of pressure required to effect a passage at a certain rate.

(2) **THE TRANSLATORY MOVEMENT OF IONS AND MOLECULES.** This is identical with the osmotic pressure of these ions and molecules since, as we have seen, the osmotic pressure is due to the continual movement of molecules and can be compared to a bombardment on the walls of the vessel by the atoms or molecules present. In solution the molecules can move freely only within the limits of the solution. Diffusion is due to this movement. The rate of diffusion is not the same for all substances. In gases the rate varies inversely as the square root of the density of the gas. We find similar differences between the rates of diffusion of dissolved substances—differences which also are determined in all probability by the weight and size of the individual molecules, although the relation between molecular weight and rate of diffusion is not so simple as the ratio between these two quantities in gases.

The diffusibility of a substance is given by its *diffusion coefficient*. The amount of dissolved substance, which diffuses in a unit of time across a given area of fluid, is proportional to the difference between the osmotic pressures at two cross sections of the column of fluid at an infinitesimally small distance apart. If we take a cylindrical mass of solution which is one centimetre long and has a sectional area of one square centimetre (Fig. 24), and maintain a constant difference of concentration between A and B = 1, the diffusion coefficient is the

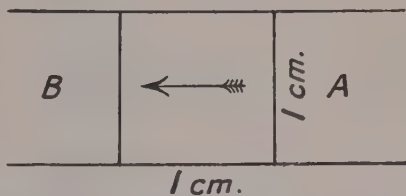


Fig. 24.

amount of substance which diffuses in a unit of time from A to B. Thus the statement that the diffusion coefficient of urea is 0.810 at 7.5° C. denotes that, if A be continually filled with a 1 per cent. solution of urea, while in B a constant current of distilled water is kept up so as to maintain the concentration at zero, in the course of a day 0.810 gramme of urea will pass from A to B through the cylinder of one centimetre in length and one square centimetre in cross section. The determination of these diffusion coefficients presents many difficulties. The task is however rendered easier by the fact, first ascertained by Graham, that diffusion of salts occurs as rapidly through a solid jelly of gelatine or agar-agar as through water. It is therefore possible to make the plug in the diagram solid by the admixture of one of these two substances, and to maintain a constant concentration on the two sides of it by the circulation of fluid without affecting the rate of diffusion through the cylinder by setting up accidental currents.

If a layer of distilled water be poured carefully on to the top of a strong salt solution, the salt will gradually diffuse from the bottom into the top layer, but it will take a long time before the composition of the fluid has become the same throughout. The molecules of salt, dissociated and undissociated, tend to move straight up into the upper layer but are continually

meeting the molecules of water and rebound from these, so that it is only by slow degrees that the salt molecules under their own movement make their way through the crowd of water molecules so as to become evenly distributed throughout. If the upper fluid contains, say, sugar and the lower fluid salt, these will both move in opposite directions until homogeneity is attained. This equalisation of the solid contents of two fluids is not altered by placing between them a membrane freely permeable both to the water and the dissolved substances; if sufficient time be given, the fluids on the two sides of the membrane will attain identical compositions. There may however be different initial distributions and temporary alterations of the distribution of the total fluid on the two sides of the membrane, due to varying rates of diffusion of the dissolved substances.

If in Fig. 25 for instance A contains a solution of sugar and B an isosmotic solution of NaCl, separated by a membrane freely permeable both to water and to these substances, the salt will diffuse from B to A more rapidly than the sugar will diffuse from A into B. There will thus be a tendency to a rise of the total osmotic pressure in A which will determine a passage of water from B into A. This will cause an initial increase of the total fluid in A and a diminution in B or, if both compartments are closed, the pressure in A will rise above the pressure in B. This rise of pressure in

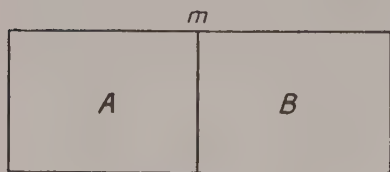


FIG. 25.

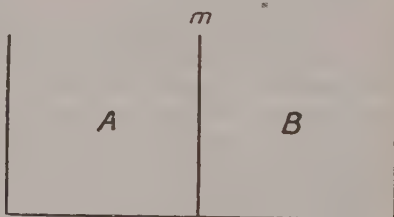


FIG. 26.

A will cause a filtration of the whole fluid from A to B, so that in time we shall attain equilibrium both of pressure and of contents between A and B. The time taken to attain this equilibrium will vary with the thickness of the membrane, and with a membrane of molecular dimensions and compartments of microscopic size the equilibrium will be attained almost instantly, so that the effects of 'initial osmosis' may be disregarded.

(3) ELECTRICAL DIFFERENCE OF POTENTIAL. This factor probably plays an important part in the transference of dissolved substances across membranes in the body. Just as differences of hydrostatic pressure determine movements of a fluid *en masse*, differences of electric pressure will serve as a driving force for the charged constituents of fluids. These may be actual particles, *e.g.* oil droplets or bacteria, the ultra-microscopic particles of colloids or the ions derived from the electrolytic dissociation of dissolved molecules. The passage depends on the fact that any charged particle will move in an electric field, the positive particle moving towards the negative pole while the negatively charged particle moves towards the positive pole. The electricity passing through the fluid is in fact carried by the particles which are thus set into movement. If a current is passed across a membrane immersed in an electrolyte, as in the diagram (Fig. 26), the final result will be a chemical difference on the two sides and therefore a permanent difference of potential which will tend, on breaking the current, to drive the ions in the opposite direction and to re-establish equilibrium on the two sides. The process of

passage of a current across a membrane is said thus to give rise to polarisation, and after the passage of the current the membrane is polarised, *i.e.* presents a difference of potential between its two sides.

A charge on a membrane may cause a passage of water with an electric current through the membrane. This may be explained as follows: A charged particle, if free to move, will travel to the pole with the opposite charge; thus clay is negatively charged and migrates to the anode. Suppose now in Fig. 26 that *m* is made of clay and that electrodes are immersed

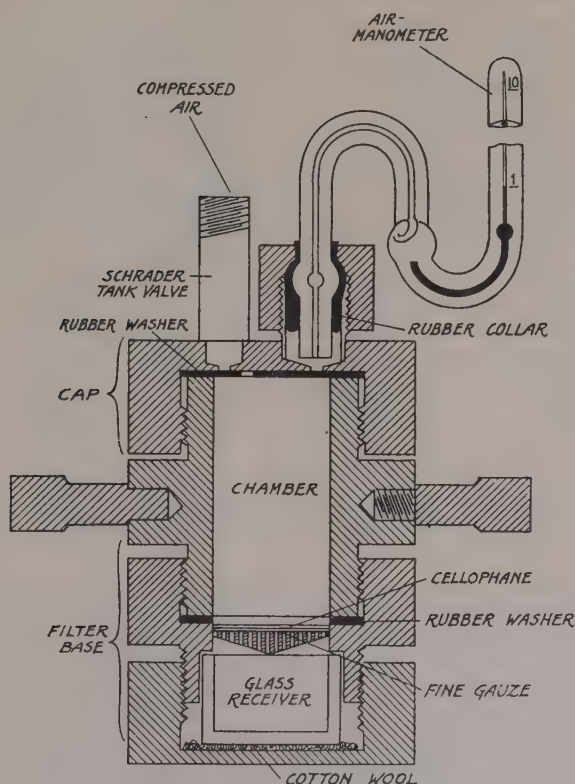


FIG. 27. Apparatus for ultra-filtration. The filtering membrane is cellophane. The upper chamber contains the colloid solution, which is forced through as a colloid-free filtrate into the lower chamber. The requisite pressure is provided by a motor-tyre pump. (KAY.)

in the fluid, the anode in A and the cathode in B. Now since the clay partition is fixed the water moves instead, *viz.* to the negative pole, so that the volume in B is increased. This phenomenon is called *electro-endosmosis*. With a gelatine membrane, the charge depends on the reaction of the solution. If this is alkaline, the gelatin is, like clay, negatively charged, but if acid it is positively charged and the direction of the flow is reversed.

(4) PERMEABILITY OF THE MEMBRANE. The nature of the membrane cannot add to the force concerned in the transference of water or dissolved substances across it: it can only serve as a limiting condition for the action of the forces just enumerated. How these forces will act in regard to different

kinds of membrane will depend on the permeability of the membrane, and this again on its physical and chemical structure. The membrane may be absolutely impermeable, as in the case of mica or glass. Such membranes are found surrounding certain eggs, and in plants as a means of protection for seeds. In most cases however the permeability is relative. Filter paper for instance permits the passage both of water and of all dissolved substances. Different kinds of filter paper allow passage with varying degrees of rapidity, depending on the fineness of grain, *i.e.* on the size of the holes through which the fluid can pass. The same difference may be observed in porous structures, such as the Berkefeld filter, which allow all dissolved substances to pass but keep back most bacteria. On the other hand the very smallest micro-organisms, the so-called filter passers, will traverse the pores of a Berkefeld filter. Most gels, such as gelatin and collodion, can be regarded as a network of fibres or as a honeycomb, the meshes or cavities in which are filled with the fluid with which the membrane is impregnated. Bechhold has shown that collodion membranes may be obtained of varying degrees of permeability according to their mode of preparation and the concentration of the collodion in the membrane. Such membranes are used for the process of what is known as *ultra-filtration*. The membranes of looser texture will allow proteins such as albumin to pass in addition to crystalloids. On the other hand the denser collodion membranes, or cellophane, will keep back all colloid constituents and allow only water and salts to pass. If for instance serum be placed on one side of such a membrane, under pressure a filtrate will be obtained containing the water, salts, urea and other crystalloid constituents of the serum (Fig. 27).

A still greater degree of impermeability is obtained with "semi-permeable" membranes such as the colloidal precipitate of copper ferrocyanide, which is found to prevent the passage of a large number of dissolved substances.

Finally we may have a form of permeability which depends on the solubility of the solute in the membrane itself, or on the formation of reversible compounds between the solute and the membrane. Thus indiarubber dissolves carbon dioxide. If a rubber balloon containing air be placed in a vessel filled with carbon dioxide, the balloon rapidly expands and may even burst. The carbon dioxide molecules are dissolved in the rubber and diffuse on the other side into the air inside the bag. The molecules of nitrogen and oxygen cannot pass in the reverse direction, so that the balloon approaches a point at which it contains carbon dioxide in addition to the air which it contained at first, so that it dilates till it bursts. A vessel consisting of palladium permits the easy transit of hydrogen, so that if immersed in an atmosphere of hydrogen the pressure in its interior rises rapidly. This may be a question of solution or may be due to the formation of a reversible compound between the hydrogen and the palladium.

Of these different kinds of membrane two are of special physiological importance: those which are impermeable to colloids but allow free passage to crystalloids, and those which are more or less impermeable to certain crystalloid molecules. Some colloidal membranes, such as gelatin, parchment paper and collodion, belong to the first of these classes. They can be regarded as formed of a fine colloidal network or honeycomb containing water in the meshes. These allow a free passage of salts but hold back such large molecules as are colloidal or semi-colloidal. They are thus made use of when it is desired to free a colloidal solution from salts, as in the process known as *dialysis*. If a fluid containing both colloids and crystal-

loids in solution, *e.g.* blood serum, be enclosed in a tube of vegetable parchment or collodion which is hung up in a large bulk of distilled water (Fig. 28), all the salts diffuse out, and if the water be frequently changed, we obtain finally a fluid within the 'dialyser' free from salts and other crystalloid substances, but containing the whole of the colloidal proteins originally present. If a certain pressure is put on the contents of the dialyser, or (as in Fig. 28) suction on the outside, fluid also passes out by ultra-filtration, but there is a certain limiting pressure below which no filtration will take place. This limiting pressure is equivalent to the osmotic pressure of the colloids in solution, and varies according to the state of aggregation of the colloid, *i.e.* to the number of molecules, simple or compound, of the colloid which is present. In blood serum it is equal to about 30 mm. Hg. If the difference of pressure on the two sides of the membrane is less than this amount, water and salts will pass from the outside to the inside of the membrane and the serum will be diluted.

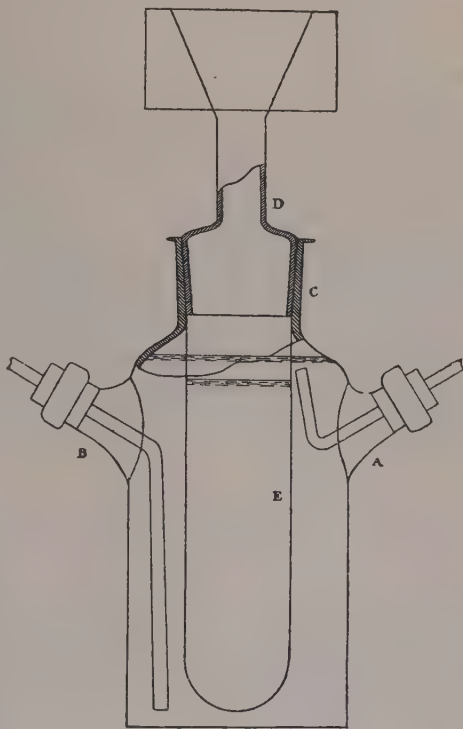


FIG. 28. Dialysing Apparatus. The collodion tube E is fastened to the glass stopper D which fits airtight into the neck of the bottle C. Sterile water is introduced into the bottle from a reservoir through B, and the colloid for dialysis poured into E. A partial vacuum is then made in the bottle by exhaustion at A; this opposes the osmotic pressure of the solution in E and so prevents its dilution, or if great enough may even concentrate it by ultra-filtration. (JESSEN HANSEN.)

(5) MEMBRANE EQUILIBRIA.

If the colloid is in the form of a compound with either acid or base, which undergoes ionic dissociation, certain interesting results are observed. For instance, Congo red is a compound of an indiffusible colloid acid with

sodium. If this be placed in an osmometer which is immersed in water, a certain osmotic pressure is developed. Although sodium ions can pass readily through the membrane of the osmometer, they carry a positive charge, so that if they broke away from their combination with Congo red acid, the fluid in the osmometer would become negatively charged. The sodium ions are thus held in the immediate neighbourhood of the membrane by the electrostatic attraction between Congo red acid ions and the sodium ions. If we add sodium chloride either to the inner or outer fluid, the osmotic pressure is found to fall if time be allowed for equilibrium to be established between the two sides of the membrane. At this point the outer fluid, which is free from dye, contains a larger percentage of sodium chloride than the inner fluid. This difference is permanent and is more marked the greater the concentration of the dye. In the following Table are given the concentrations of the two fluids with different percentages of salts, the

numbers indicating the litres to which each gramme molecule of the salt is diluted.

Dye.							Inside.	Chlorine.	Outside.
30 .	.	.	.	.	.	.	52	..	30
30 .	.	.	.	.	.	.	465	..	73.6
30 .	.	.	.	.	.	.	5500	..	180
100 .	.	.	.	.	.	.	32.9	..	29.5

These facts were experimentally determined by Bayliss. Donnan independently showed that these results must occur from thermodynamic considerations, so that their general statement is spoken of as the 'Donnan equilibrium.'

When a saline solution contained in a collodion sac is suspended in a beaker of distilled water, the simple laws of diffusion suffice to explain the final equal concentrations of salt reached on both sides of this permeable membrane. If however a sodium salt of a non-diffusible anion (R) be placed on one side of a dialysing membrane and pure water on the other side, simple osmosis does not suffice to explain the final state of equilibrium. The Na will tend to pass through the membrane, but this can only take place if an equivalent quantity of OH (from the water) diffuses in the same direction. Thus :

Initial State			Final State		
Na	pure water		Na	Na	
R			H	OH	
			R		

The solution in the left compartment will thus become less alkaline. Again if NaR be placed on one side of the membrane and NaCl on the other side, equilibrium will be attained only when the products of the concentrations of [Na] and [Cl] are the same on opposite sides of the membrane.

Initial State			Final State		
Na	Na		Na	Na	
	Cl		Cl	Cl	
R			R		

$$[\text{Na}]_1 \times [\text{Cl}]_1 = [\text{Na}]_2 \times [\text{Cl}]_2$$

This can only occur if $[\text{Na}]_1 > [\text{Na}]_2$ and $[\text{Cl}]_1 < [\text{Cl}]_2$.

This difference in the concentration of the diffusible ions on opposite sides of the membrane gives rise to a potential difference which is equal to

$$58 \log. \frac{[\text{Cl}]_1}{[\text{Cl}]_2} \text{ millivolts.}$$

Since many of the compounds in the body are of the form NaR, *e.g.* sodium proteinate, and the living tissues abound in membranes impermeable to colloids, Donnan's theory of 'membrane equilibria' must have a wide application in physiology.

(6) CONDUCTIVITY AND OTHER PROPERTIES OF MEMBRANES. The presence of a membrane impermeable to the colloidal constituent of an ionised colloidal salt will affect the passage of a current through the membrane in one direction, so that the phenomenon of 'irreciprocal conductivity' is presented. Thus if in Fig. 29, A contains the potassium salt of hæmoglobin and B contains potassium chloride, a current can pass from

A to B, since it is carried from A to B by the potassium ions which can pass freely through the membrane, and from B to A by the electro-negative ions, namely chlorine. An application of this method called *electro-dialysis*, is in fact one of the best ways of freeing protein solutions from adsorbed basic ions. If however B be made the positive pole, no current can pass because the electro-negative ion, namely hæmoglobin, cannot pass through the membrane *m*. If we take an arrangement with three compartments A, B and C, of which only B contains

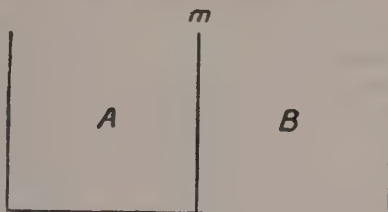


FIG. 29.

a protein salt, the passage of a current will be hindered in both directions since, whichever the direction of the current, the protein molecule will be required to carry the negative electricity either into A or into C. This resistance to the passage of a current will be still more marked if the membrane is impermeable also to certain inorganic ions. It is on this account that whole blood presents a greater resistance to the passage of a current than does the serum itself, each of the red blood corpuscles serving as a non-conductor and therefore diminishing the total area through which the current can pass.

No completely semi-permeable membrane is known, *i.e.* one which allows the passage of water but is impermeable to all dissolved substances. The best known artificial semi-permeable membrane is that composed of copper ferrocyanide, supported in the meshes of a clay cell. This membrane is impermeable to copper salts, to ferrocyanides, to sugar and to certain other dissolved substances: it permits KCl however to pass freely. Its semi-permeability may be increased by depositing AgCl, when it becomes impermeable also to potassium chloride. Such membranes are of much interest since, as already mentioned, the surfaces of all cells show in greater or less degree the phenomenon of semi-permeability. Thus red blood corpuscles are impermeable to most kations, such as Na, K and Ca and perhaps also to sugar, but allow the passage of urea, CO₂, chlorine ions and OH ions as well as NH₄. Cell surfaces are freely permeable to a number of organic substances, namely those which are soluble in lipides such as the alcohols. It has therefore been suggested by Overton that the limiting membrane is lipoidal in nature, formed *e.g.* of a mixture of lecithin and cholesterol. It is true that these substances take part in the formation of the membrane, which may be regarded as a surface aggregation of molecules forming part of the contents of the protoplasm within the cell; but it seems certain that proteins also take part in the formation of this membrane, and that in some way its integrity is dependent on the presence of certain salts in the outer fluid which may be adsorbed on the external surface of the membrane and so contribute to its qualities. Thus many cells, such as egg cells, muscle cells, entirely alter their permeability if immersed for a time in a fluid free from Ca salts, and under these circumstances may become permeable to substances such as KCl, which they do not ordinarily allow to pass. The surface membrane of a cell differs, however, from our artificial semi-permeable membranes in that its qualities of permeability are variable according to the state of the cell itself and to its metabolic requirements. Thus activity of a cell is always attended with an increased permeability of its surface membrane, and this change in permeability may in the case of muscle be the responsible factor for the transformation of shape, which

represents the function of the muscle fibre. Although cells are impermeable to sugar and many acids, yet they take up these substances from the medium in which they exist as required by their metabolic needs, so that any description which we can give of the permeability of a living cell must be regarded as applicable only to its state of rest under average conditions. The membrane must change its chemical and physical characters with every change in the environment and with every change in the state of the activity of the cell. It is this dependence of permeability on cell function that must be made responsible for the wide differences observed between the composition of a cell and that of its surrounding medium. The red blood corpuscles for instance are rich in potassium salts and may contain no sodium salts, whereas the reverse holds good for the blood plasma in which they are bathed. Both the red blood corpuscles and the plasma contain glucose, but there is no constant relation between the amounts of glucose in the two.

How this change is effected we do not know. One suggestion is that an alteration in the structure of the membrane may sometimes account for it. Such an alteration would take place if a colloidal membrane underwent a *reversal of phases*, e.g. it might change from an emulsion of oil in water to one of water in oil: the former would be permeable to substances soluble in water, the latter to those soluble in oil. Such a reversal is believed to take place when an emulsion of oil is treated with traces of calcium salts. Another structural alteration which might be possible would be one associated with an alteration in the orientation of the molecules in a monomolecular film.

Not only does the function of the cell determine the properties of its surface but the reverse holds true. Cell activities seem to be determined to a very large extent by the presence of substances in the surrounding medium which cannot penetrate the limiting membrane of the cell. This is especially well-marked in the case of contractile tissues such as the heart where, as we have seen, the normal beat depends on the presence in the surrounding fluid of K, Na and Ca ions. None of these can penetrate the cell membrane so as to gain access to the interior of the cell: they can merely be adsorbed on the cell surface, and it is their presence there which in some way or other determines all the functional activities of the muscle cell.

In nearly every case the hindrance to migration of one or more ions by the membrane will prevent the passage of other associated ions to which by themselves the membrane would be freely permeable. These ions will travel an infinitesimal distance through the membrane till they are held back by the electrostatic attraction of the oppositely charged ions which cannot pass. This electrostatic tension will give rise to a charge on the surface of the cell, and in nearly every case free swimming cells such as red blood corpuscles are found to be charged differently from the solution in which they are suspended. In most cases this charge is negative, so that, if a current be passed through blood, the red blood corpuscles will tend to travel towards the positive pole. In the course of this work we shall have many further opportunities of studying the dependence of function upon the properties of the cell surface with which in this chapter we have dealt in general terms.

THE ENERGETIC BASIS OF THE BODY

CHAPTER IX

ELECTRICAL CHANGES IN LIVING TISSUES

THE material composing living cells and tissues is permeated throughout with water containing electrolytes in solution. All salts, as we have seen, undergo ionic dissociation in watery solution—a dissociation which, in the concentrations occurring in the animal body, must be nearly complete. When an electric current passes through the living tissues it is carried by the charged ions formed by the dissociation of the salts. Thus N/10 solution of sodium chloride contains almost entirely Na^+ and Cl^- ions. In addition to these charged inorganic ions, the cell protoplasm contains in solution or suspension various colloidal particles which in many cases are themselves charged. By the presence of these colloidal particles, marked differences may be caused in the distribution of the inorganic ions owing to the power of adsorption possessed by the colloids for many inorganic salts. Any unequal distribution of the charged ions or colloidal particles in a tissue or on the two sides of a membrane may give rise to corresponding unequal distribution of electric charges, and therefore differences of potential between parts of the tissue, which under suitable conditions may find their expression in an electric current. It is therefore not surprising that practically every functional change in a tissue has been shown to be associated with the production of differences of electrical potential. Thus all parts of an uninjured muscle are isopotential, and any two points may be led off to a galvanometer without any current being observed. If however one part of the muscle be strongly excited, as for instance by injury, so that it is brought into a state of lasting excitation, it will be found that, on leading off from this point and a point on the uninjured surface to a galvanometer, a current flows through the latter from the uninjured to the injured surface. Every beat of the heart, every twitch of a muscle, every state of secretion of a gland is associated in the same way with electrical changes. In most cases the electrical changes accompanying activity have the same general character, the excited part being found to be galvanometrically negative in reference to any other part of the tissue which is at rest. The uniform character of the electric response in different kinds of tissue suggests that an accurate knowledge of the changes in the distribution of charged ions, of which the response consists, ought to throw important light on the intimate nature of excitation generally. It may be therefore advisable to consider more closely the conditions which determine differences of potential in a complex system of electrolytes.

As a simple case we may take an ordinary concentration cell. Two vessels (Fig. 30), A and B, are united by a glass tube C. A contains a 10 per cent. solution of zinc sulphate and B a 1 per cent. solution of the same salt. A rod of pure zinc is immersed in each limb. On connecting the zincs

to a galvanometer G, a current is observed to flow from A to B through the galvanometer, and therefore from B to A through the cell. A solution of zinc sulphate contains partly undissociated ZnSO_4 and partly dissociated Zn^{++} and SO_4^{--} ions. If a rod of zinc be immersed in a watery fluid, the zinc tends to dissolve. The Zn passing into the fluid is however immediately ionised, and therefore carries a positive charge into the fluid, leaving the zinc negatively charged (Fig. 31). The positively charged ions in the fluid will tend to repel back into the zinc any ions which may be escaping from the zinc, and the process of solution will come to an end as soon as the osmotic pressure of Zn^{++} ions in the solution equals the tendency of the zinc to go into solution, which is called the electrolytic solution pressure. If the value of Zn^{++} ions in solution exceeds this, then Zn tends to be deposited on the rod instead of dissolved.

The less the original concentration of Zn^{++} ions in the solution the more will dissolve from the rod, and hence the more negatively charged this will

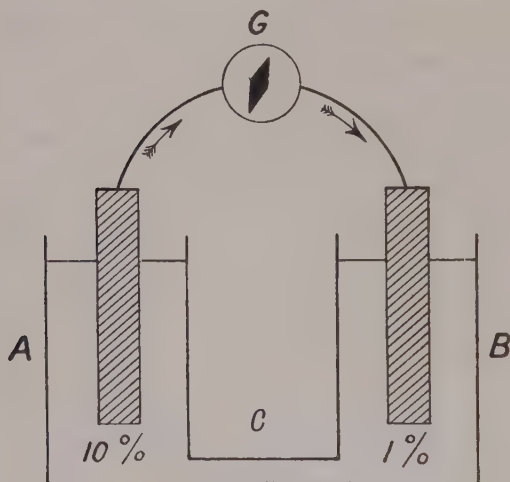


FIG. 30.

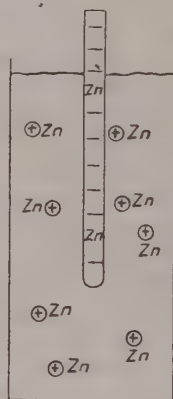


FIG. 31.

become. Hence in B the zinc will be more negative than in solution A. When the two zincs are connected together, negative electrons pass along the wire from B to A and Zn^{++} ions are deposited on the Zn in A to neutralise these; the SO_4^{--} ions so set free migrate into B, to equalise the positive changes on the zinc ions; more zinc dissolves in B until finally the concentrations in the two cells are equal, when the current ceases. In this process no chemical energy is involved, the energy set free by the conversion of zinc into zinc sulphate in B being exactly balanced by the energy lost by the deposition of zinc from zinc sulphate in A. Yet the current which is produced has a certain amount of energy which can be utilised for heating a wire through which it is made to pass. Since this energy must be taken from the cell, the cell is cooled during the passage of the current. We have here a close analogy with the case of compressed gases. If the 10 per cent. and 1 per cent. solutions were mixed together in a calorimeter, no change of temperature would be produced, since no work is done in the process. In the same way no cooling effect is observed if compressed gas be allowed to expand into a vacuum. If however the compressed gas be allowed to expand from a narrow orifice against the pressure of the external air, so that it does work in

the process, it is cooled; and this cooling effect is made use of in the working of refrigerating machines or for the liquefaction of gases. We may therefore regard the concentration battery as a machine for making the substances in solution do work as they expand from a strong into a dilute solution.

In the ordinary Daniell galvanic cell, negative electrons pass through the wire from zinc to copper and copper is deposited from CuSO_4 solution on to the copper plate. The SO_4^{--} ions thus set free migrate to the other cell and equalise the Zn^{++} ions set free by solution of the zinc, which is thus able further to dissolve.

The differences of potential obtained from an ordinary concentration cell are very small and would not suffice to account for such a high electromotive force as is set up *e.g.* in the contraction of a muscle. We have seen earlier that even in isosmotic solutions differences of pressure may be brought about by differences in diffusibility of the substances in solution, especially if the two solutions be separated by a membrane. Very large differences may be produced if this membrane be practically impermeable to one or other of the dissolved substances. In the same way a semipermeable membrane *i.e.* a membrane with different permeabilities for the ions of the two solutions, may suffice to bring the differences of potential of a concentration cell up to and beyond the extent which is observed in living tissues. Supposing we have (Fig. 32) two solutions, A and B, each containing an electrolyte, UV, in different concentrations separated by a membrane *m*. If *u* represents the velocity of transmission of U through *m*, and *v* the velocity of V, then the electromotive force of the cell is given by the formula :

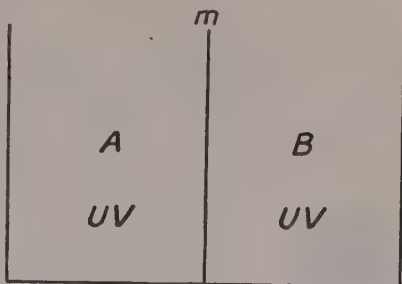


FIG. 32.

$$\frac{u - v}{u + v} 0.0577 \log_{10} \frac{c_2}{c_1} \text{ Volt.}$$

If *v* is taken as very small, the membrane may be regarded as semipermeable for the corresponding ion V. Supposing we take potassium chloride as the solution, we should have to make the concentration in B eight times that in A, in order to get a current of strength equal to that obtained from the olfactory nerve of the pike, for example. Macdonald has made such an assumption in order to explain the normal nerve current. He suggests that the axis cylinder contains an electrolyte which is equivalent to a 2.6 per cent. solution of potassium chloride. It is unnecessary however to assume such great differences of concentration if we regard the membrane as itself a solution of electrolytes, as suggested by Cremer, or if we take different substances on the two sides of the membrane. In the case of two electrolytes U_1V_1 , U_2V_2 (U being the kation in each case), separated by a membrane with varying permeability for the different ions, the electromotive force of the cell is given by the following formula :

$$0.0577 \log_{10} \frac{u_1 + v_2}{u_2 + v_1}$$

where u_1 , v_1 , u_2 , v_2 are the velocities of the corresponding ions. We assume that the concentrations of the two solutions are identical. Now

by making u_2 and v_1 very small, the expression $\log_{10} \frac{u_1 + v_2}{u_2 + v_1}$ may be made to attain any quantity, and in the same way by making $u_1 + v_2$ infinitesimally small, the electromotive force of the combination will also become correspondingly small. The thickness of the membrane does not come into the formula, so that membranes of microscopic or even ultra-microscopic thickness, which we have seen reason to assume as present in and around cells and their parts, could perform all the functions required of the hypothetical membrane in the above example. This is also the case when V_1 is the same as V_2 —that is to say, there is a common anion or a common kation on the two sides of the membrane.

It must be remembered that the passage of a current through a membrane impermeable to one or other ion in the surrounding fluid will cause an accumulation of the ion at the surface of the membrane, so that this will become polarised. Such an accumulation at any surface will naturally alter its properties, including its surface tension. The construction of the capillary electrometer depends on this fact. When mercury is in contact with dilute acid or mercuric sulphate solution, it takes a positive charge from the fluid, and the state of stress at the surface of contact between the mercury and the negatively charged fluid diminishes the surface tension of the mercury. If the mercury be in the form of a drop in a tube drawn out to a capillary, the mercury will run down the capillary and the drop will be deformed until the surface tension tending to pull the mercury into a spherical globule is just equal to the force of gravity tending to make the mercury run out through the end of the capillary (Fig. 33). If the mercury be immersed in sulphuric acid, it will descend to a lower level in the capillary owing to the diminution of its surface tension. If now the acid and the mercury be connected with a source of current so as to charge the mercury negatively, the effect will be to diminish the charge previously taken

FIG. 33.

up by the mercury. The state of tension at the contact with the acid is therefore diminished, the surface tension is increased, and the mercury withdraws itself from the point of the capillary. If however the mercury be connected with the positive pole, its charge will be increased and its surface tension correspondingly diminished, so that the meniscus will move towards the point of the capillary. The movement of the meniscus towards or away from the point may thus be used, as in the capillary electrometer, to show the direction and amount of any moderate electric change occurring in a tissue, two points of which are connected with the mercury and the acid respectively. It is possible that this electrical alteration of surface tension may have some part to play in many of the phenomena of movement observed in the animal body. We shall have occasion to discuss this question more fully when endeavouring to account for the ultimate nature of muscular contraction.

THE ENERGETIC BASIS OF THE BODY

CHAPTER X

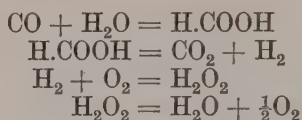
THE MECHANISM OF CHEMICAL CHANGES IN LIVING MATTER

ALL the events which make up the life of plants and animals are accompanied and conditioned by chemical changes of the most varied character. In a previous chapter we have endeavoured to form an idea of the ways in which some of the synthetic processes that occur in the living body may be effected. We saw that, although it was possible to imitate in many respects the vital syntheses by ordinary laboratory methods, the imitation fell far short of the process as it actually occurs in the living cell, both in completeness of the reaction and in the ease with which it could be effected. We can for instance, by passing carbon dioxide over red-hot charcoal, convert it into carbon monoxide, and this gas, acting on dry potassium hydrate, forms potassium formate. Calcium formate, on dry distillation, gives a small proportion of formaldehyde which, under the influence of dilute alkalies, will condense to the mixture of sugars known as acrose. The green leaf in sunlight absorbs the minimal quantities of carbon dioxide present in the atmosphere and converts it almost quantitatively into starch within a few minutes, and this change is effected in the absence of any concentrated reagents and at the ordinary temperature of the atmosphere. Many of the chemical transformations effected by living cells we have so far been quite unable to imitate. The problem of the synthesis of proteins, of the terpenes, of starch, of cellulose, is still unsolved; and even in the case of those substances which we can manufacture outside the living cell, our methods involve the use of powerful reagents and of high temperatures, and result in most cases in the production of many side reactions, besides that reaction which it is our special object to imitate. The distinguishing characteristics of the chemical changes wrought by the living cell are:

- (1) The rapidity with which they are effected at ordinary temperatures.
- (2) The specific direction of the process, which is therefore almost complete, with a surprising absence of the side reactions which interfere to such an extent with the yield of the methods employed in a chemical laboratory. This characteristic may however be regarded as a consequence of the first, since an increase in the velocity of any given reaction will determine a preponderance of this reaction over all other possible ones. A fundamental question therefore in physiology must relate to the manner in which the cell is able to influence the velocity of some specific reaction.
- (3) The production of optically active substances when possible.

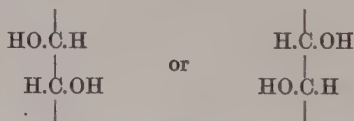
The essential condition of all chemical changes in living beings is that they take place in a watery medium. When the cell is deprived of water, it is either killed or enters into a state of inactivity, and in many

cases active metabolism and growth can be re-established by the agency of water, as for instance in the germination of seeds. But it is not only as a medium that water is essential. It seems that the water molecule itself is involved in every chemical change that occurs. It must be acknowledged that this statement is not wholly distinctive of chemical changes in the cell, since many of the ordinary reactions of inorganic and organic chemistry, such as the explosion of mixtures of oxygen with combustible gases, have been shown to be dependent on the presence of traces of water. Thus the oxidation of carbon monoxide to CO_2 by means of oxygen takes place in the following phases:—

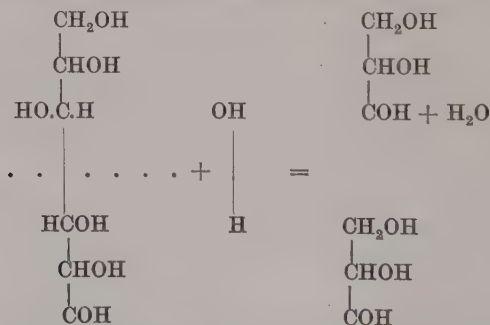


formic acid and hydrogen peroxide having been actually isolated as intermediate products. But whereas in a case such as this the presence of mere traces of water is sufficient, in the living cell water seems to play the chief part in every reaction, and the reactions themselves take place as a rule in very dilute solutions.

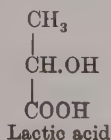
The water molecule H_2O dissociates into the ions H and OH . Apparently the molecule may act as a whole or the H and OH ions may be separately involved. In many cases the interaction of the water molecule is not apparent in the simplest method of expressing the chemical change by an equation. Thus sugar $\text{C}_6\text{H}_{12}\text{O}_6$ splits up under various conditions into two molecules of lactic acid $\text{C}_3\text{H}_6\text{O}_3$. This occurs under the action of many micro-organisms: in the case of glucose, fructose and mannose the atoms round the two middle carbon atoms of the chain are disposed thus:



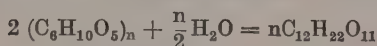
When either of these arrangements reacts with water thus:



we obtain two molecules of glyceric aldehyde, which then by a further shifting of the OH and H groups becomes



In each of these stages the water molecule is involved, entering the molecule at one part but leaving at the same time at another, so that finally the essential interaction of water in the process does not appear in the equation. In either case, as in hydrolysis, the water is added to the molecule on which it acts, with the production of a hydrated product or with a splitting of the original molecule into two parts as a result. The rapidity with which these changes occur in the body is very striking, especially when we consider the apparent chemical inactivity of water itself. Thus if we take a solution of boiled starch into the mouth, keep it there for twenty seconds and then eject it, the fluid is found to contain no starch but to contain maltose. In this case there has been a taking up of water molecules by the starch, so that the interaction of water appears in the equation—



On the other hand a solution of boiled starch in water may be left for many weeks or months without undergoing this change, which however can be induced by heating the fluid in an autoclave to 120° C. for several hours. There must be some means by which the action of the water on the starch is quickened to such an extent that the process of hydrolysis occurs at the temperature of the body even more rapidly than it occurs in the autoclave. In the body this process of quickening the velocity of chemical change in certain definite directions is carried out by means of *enzymes*.

ENZYMES

Under the name enzymes or ferments we include a number of substances of indefinite composition whose existence is known to us only by their action on other substances. An enzyme has been defined as an organic catalyst produced by a living organism. It differs therefore from the reacting substances in the absence of any strict quantitative relationships between it and the substances included in the system on which its effects are produced. Minimal quantities of enzyme can induce chemical changes involving almost indefinite quantities of other substances, the only result of increasing the quantity of enzyme being to quicken the rate of the change. Since they are effective in minimal doses, they occur in living tissues in minute quantities, and it is partly due to this fact that it has hitherto proved impossible to obtain any preparation of an enzyme which can be regarded as a pure substance. The difficulty in their isolation is increased by the fact that all of them are colloidal or semi-colloidal in character, and present the tendency common to all colloids of adhering to other colloidal matter as well as to surfaces such as those presented by a precipitate. A common method of obtaining a concentrated preparation of an enzyme is to add to its solution a strongly adsorbing colloidal precipitate, such as alumina or kaolin. The enzyme is carried down on the precipitate and may be obtained in solution by treating this with water or dilute alkali. By fractional adsorption with different adsorbents, enzymes may be greatly concentrated and also separated from one another. A further difficulty in their preparation lies in the unstable character of many members of the group, so that every act of precipitation of an enzyme tends to rob it of some of its powers.

Of these enzymes a large number have already been described as taking part in the ordinary chemical processes of life. So wide is their dominion in cell chemistry that many physiologists have thought that the whole of life is really a continual series of enzyme actions. The following list repre-

sents some of the ferments whose existence has been definitely established in the animal body. The greater number of them are involved in the processes of digestion in the alimentary canal. The preponderance however of digestive enzymes in the list is due to the fact that we know more about digestion than about the other enzyme actions taking place within the cells of the body.

LIST OF ENZYMES

Enzyme	converting	into
Amylase (of saliva, pancreatic juice, liver, blood serum, &c.)	Starch	Maltose and dextrin
Pepsin	Proteins	Proteoses and peptones
Trypsin	Proteins	Peptones and amino-acids
Phosphatase (bone, kidney, intestine)	Phosphoric esters	Hydrolysed
Erepsin	Proteoses	Amino-acids
Lipase (of pancreatic juice, liver, &c.)	Neutral fats	Fatty acid and glycerin
Maltase	Maltose	Glucose
Lactase	Milk sugar	Glucose and galactose
Invertase or sucrase	Cane sugar	Glucose and lævulose
Arginase	Arginin	Urea and ornithine
Urease	Urea	Ammonium carbonate
Lactic acid enzyme	Glucose	Lactic acid
Zymase (? present in the body)	Glucose	Alcohol and GO_2
Deaminating enzyme	Amino-acids	Oxy-acids (?)

Many other enzymes will probably be distinguished with increase in our knowledge of cellular metabolism. The list which is here given suffices to show how great a part these bodies must play in the normal processes of life. A study of the conditions of enzyme actions is therefore essential if we would form a conception of the chemical mechanisms of the living cell.

It is important to note that all the changes wrought by enzymes can be effected by ordinary chemical means. Thus the disaccharides can be made to take up a molecule of water and undergo conversion into monosaccharides. If a solution of maltose be kept and bacteria be excluded from the solution, it undergoes at ordinary temperatures practically no change. If the solution be warmed, a slow process of hydration takes place which is quickened by rise of temperature, so that if the solution be heated under pressure to, say, 110°C ., hydrolysis occurs with considerable rapidity. If however a little maltase be added to the solution, the change of maltose into glucose takes place rapidly at a temperature of 30°C . In the same way a solution of protein may be kept almost indefinitely without undergoing hydrolysis, which however can be induced by heating the solution under pressure. The action of the enzymes in these two cases is to quicken a process of hydrolysis which without their presence would take an infinity of time for its accomplishment.

CATALYSIS.—In this respect their action is similar to that of acids, and indeed of a whole class of bodies which are spoken of as *catalysers* or *catalysts*. A catalyser is a substance which will increase (or diminish) the velocity of a reaction without adding in any way to the energy changes involved in the reaction, or taking any part in the formation of the end products. Since the catalyser is unchanged in the process, a very small quantity is able to influence reactions involving large quantities of other substances. By adding acids to a watery solution of the foodstuffs, the process of hydrolysis is quickened in proportion to the strength and concentration of the acid.

The effective catalytic agents in this process appear to be the hydrogen ions of the free acid. There are many other bodies, besides the free acids, which may act as catalysers, and a study of the conditions under which catalysis takes place may throw some light on the essential nature of the action of enzymes.

The velocity of almost any reaction in chemistry can be altered by the addition of some catalytic agent, and there are few of the ordinary reactions in which catalysis does not play some part. Among such processes we may instance the action of spongy platinum on hydrogen peroxide. Hydrogen peroxide undergoes slow spontaneous decomposition into water and oxygen. If a little spongy platinum be added to it, it is at once seen to decompose rapidly with the evolution of bubbles of oxygen. Spongy platinum is able in the same way to quicken a very large number of chemical reactions. Thus sulphur dioxide and oxygen when heated together will combine very slowly; the combination becomes rapid if a mixture of the two gases be passed over heated platinum. The same reaction, namely the combination of sulphur dioxide with oxygen, may be quickened by the addition of a small trace of nitric oxide, and this fact is made use of in the manufacture of sulphuric acid on a commercial scale by the old lead-chamber process. Hydrogen peroxide and hydriodic acid slowly interact with the formation of water and iodine. This reaction may be quickened by the addition of many substances, among which we may mention molybdic acid.

There is moreover a specificity in the action of catalysers, though not so well marked as with enzymes. Whereas all the disaccharides are converted by acids into the corresponding monosaccharides, an enzyme such as invertase acts only on cane sugar and has no action on maltose or lactose, each of which requires a specific enzyme (maltase, lactase) to effect its 'inversion.' But we find many examples of a restricted action even among inorganic catalysers. Thus potassium bichromate will act as the catalyser for the oxidation of hydriodic acid by bromic acid, but not for the oxidation of the same substance by iodic acid. Iron and copper salts in minute traces will quicken the oxidation of potassium iodide by potassium persulphate, but have no influence on the course of the oxidation of sulphur dioxide by potassium persulphate. Tungstic acid increases the velocity of oxidation of hydriodic acid by hydrogen peroxide, but has no effect on the velocity of oxidation of hydriodic acid by bromic acid, and these examples may be multiplied to any extent. One cannot therefore regard the limitation of action of the enzymes as justifying any fundamental distinction being drawn between the action of this class of substances and catalysts.

Whereas the influence of most catalysers on the velocity of a reaction increases rapidly with rise of temperature, in the case of enzymes this increase occurs only up to a certain point. This point is spoken of as the *optimum temperature* of the enzyme action. If the mixture be heated above this point, the action of the enzyme rapidly slows off and then ceases. This contrast again is only apparent. The enzymes are unstable bodies easily altered by change in their physical conditions, and destroyed in all cases at a temperature considerably below that of boiling water. Thus enzyme actions, like catalytic actions, are quickened by rise of temperature, but this effect of temperature is finally put a stop to by the destruction of the enzyme. The same applies to those inorganic catalysers whose physical state is susceptible, like that of the enzymes, to the action of heat. Thus the colloidal platinum 'sol' exerts marked catalytic effects on various reactions, e.g. on the decomposition of hydrogen peroxide and on the combination of hydrogen and oxygen. The reaction presents an optimum tem-

perature, owing to the fact that the colloidal platinum is altered, coagulated and thrown out of solution when this is heated to near boiling-point.

Very many theories have been put forward to account for this action of catalysers or of enzymes. The essential phenomena involved fall directly into two classes. In the first class we must place those which are determined by the influence of surface. In many cases the combination of gases can be hastened by increasing the surface to which they are exposed, as by passing them over broken porcelain or over powdered charcoal. This catalytic effect is certainly connected with the power of a solid to condense gases at its surface, and is therefore proportional to the extent of surface exposed. Thus the efficacy of platinum in hastening the combination of hydrogen and oxygen is in direct proportion to its fineness of subdivision, and is best marked when the metal is reduced to ultra-microscopic dimensions, as in the colloidal solution of platinum. Every colloidal solution must be regarded as presenting an enormous surface in proportion to the mass of substance in solution. The same process of condensation may occur with dissolved substances. In all cases where the presence of a substance in solution diminishes the surface tension of the solvent, there is a concentration of dissolved substances at the surface of contact. It was suggested by Faraday that the catalytic property of surfaces was due to this condensation of molecules, and the consequent bringing of the two sets of molecules within each other's sphere of influence. Whether this is the sole factor involved is doubtful, since mere compression of gases or increased concentration of solutions does not in the majority of cases result in such a quickening of the velocity of reaction as is brought about by the effect of the surface.

It is possible that this effect of adsorption may be in every case combined with the second factor which we must now consider, namely the formation of intermediate products. If we boil an alkaline solution of indigo with some glucose, the indigo is reduced with oxidation of the glucose. The mixture therefore becomes colourless. On shaking up with air, the colourless reduction product of the indigo absorbs oxygen from the atmosphere and is re-transformed into indigo. These two processes can be repeated until the whole of the glucose is oxidised, and can be made continuous if air or oxygen be bubbled through a heated solution of glucose containing a small trace of indigo. In this case the indigo does not add to the energy of the reaction : it appears unchanged among the final products, and a small amount may be used to effect the change of an infinite quantity of glucose. It therefore acts as a catalytic agent. Instead of an alkaline solution of indigo, we may use an ammoniacal solution of cupric oxide for the purpose of carrying oxygen from the atmosphere to the glucose. This is reduced to cuprous hydrate on heating with the sugar, but cupric hydrate can be at once re-formed by shaking up the cuprous solution with air. It has been thought that many or all of the catalytic reactions occur in the same way by two stages, *i.e.* by the formation of an intermediate product. Thus in the old lead chamber process for the manufacture of sulphuric acid, the nitric oxide may be supposed to combine with the oxygen of the air to form nitrogen peroxide. This interacts with sulphur dioxide, giving sulphur trioxide and nitric oxide once more. The nitric oxide, which we alluded to before as the catalyser, may in this way be regarded as the carrier of oxygen from air to sulphur dioxide. It has been suggested that the action of spongy platinum or colloidal platinum rests on the same process, and that in the oxidation of hydrogen for instance, PtO or PtO_2 is formed and at once reduced by the hydrogen with the formation of water.

But why should a reaction take place more easily if it occurs in two

stages instead of one? As Ostwald has pointed out, the formation of an intermediate compound can be regarded as a sufficient explanation of a catalytic process only when it can be demonstrated by actual experiment that the rapidity of formation of the intermediate compound and the rapidity of its decomposition into the end products of the reaction are in sum greater than the velocity of the reaction without the formation of the intermediate body. In the case of one reaction this requirement has been shown to be fulfilled. The catalytic effect of molybdic acid on the interaction of hydriodic acid and hydrogen peroxide has been explained by assuming that the first action which takes place is the formation of permolybdic acid, and that this then interacts with the hydrogen iodide to form water and iodine. Now it has been actually shown—(1) that permolybdic acid is formed by the action of hydrogen peroxide on molybdic acid; (2) that permolybdic acid with hydriodic acid produces water and iodine; (3) that the velocity with which these two reactions occur is much greater than the velocity of the interaction of hydrogen peroxide and hydriodic acid by themselves.

Although we may find it difficult to explain why a reaction should occur more quickly in the presence of a catalyser by the formation of these intermediate bodies, certain simple analogies may help us to comprehend how a factor which introduces no energy can yet assist the process. Thus a man might stand to all eternity before a perpendicular wall twenty feet high. Since he cannot reach its top at one jump, he is unable to get there at all. The introduction of a ladder will not in any way alter the total energy he must expend on raising his body for twenty feet, but will enable him to attain the top.

Since the action of enzymes, like that of catalysts, consists essentially in the quickening up of processes which would otherwise occur at an infinitely slow rate, it is possible that in their case also the formation of an intermediate compound may be involved in the reaction. Light may be thrown upon this question by a study of the velocity of the reaction induced by the action of an enzyme.

It is well known that the velocity of a reaction depends on the number of molecules involved. As an illustration, we may take first the case of a reaction involving a change in one substance. If arseniuretted hydrogen be heated, it undergoes decomposition into hydrogen and arsenic. This decomposition is not immediate but takes a certain time, and the velocity with which the change occurs depends on the temperature. At any given temperature the amount of substance changed in the unit of time varies with the concentration of the substance. If for instance one-tenth of the gas be dissociated in the first minute, in the second minute a further tenth of the gas will also be dissociated. Thus, if we start with 1000 grammes of substance, at the end of the first minute 100 grammes will have been dissociated, and 900 of the original substance will be left. In the second minute one-tenth again of the remaining substance will be dissociated, *i.e.* 90 grammes, leaving 810 grammes. In the third minute 81 grammes will be dissociated, leaving 729 grammes. The amount changed in the unit of time will always bear the same ratio to the whole substance which is to be changed, and will therefore be a function of the concentration of this substance. Put in the form of an equation, we may say that ϕ , the amount changed in the unit of time, will be equal to KC , where K is a constant varying with the substance in question and with the temperature, and C represents the concentration of the substance. The equation $\phi = KC$ applies to a monomolecular reaction.

If two substances are involved, the equation will be rather different. In this case the amount of change in a unit of time will be a function of the concentration of each of the substances, and the form of the equation will be $\phi = K(C_x \times C_y)$. In the case of the unimolecular reaction, halving the concentration of the substance will halve the amount of substance changed in the unit of time. In the case of a bimolecular reaction, halving each of the substances will cause the amount of change in the unit of time to be reduced to one-quarter of its previous amount. If now either an unimolecular or a bimolecular reaction be quickened by the addition of a catalyser or enzyme, and the latter enter into combination with one of the substances at some stage of the reaction,

our equation must take account also of the concentration of the enzyme or catalyser. In the case of the catalytic effect of molybdcic acid on the interaction between hydrogen peroxide and HI, there was definite evidence of a reaction taking place between the molybdcic acid and the peroxide, resulting in the formation of an intermediate compound, namely permolybdcic acid. Brode has shown that the interaction of the molybdcic acid is revealed in the equation representing the velocity of the reaction. Without the addition of molybdcic acid the equation would be :

$$\phi = K(C_{H_2O_2} \times C_{HI})$$

After the addition of molybdcic acid, the equation becomes :

$$\phi = K(C_{H_2O_2} + \gamma C \text{ molybdcic acid}) C_{HI}$$

when γ is another constant depending on the molybdcic acid. If enzymes act in a similar way by the formation of intermediate compounds, this fact should be revealed by a study of the velocity at which the enzyme action takes place.

Various methods may be adopted for the study of the velocity of enzyme action. If for instance we are investigating the action of diastase upon starch, we should take solutions of starch and of diastase of known concentrations, keep them in a water bath at 38° C., and at a certain point add, say, 20 c.c. of enzyme solution to every 100 c.c. of the starch solution. At periods of five or ten minutes after the addition had been made, 5 c.c. of the mixture might be withdrawn by a pipette and at once run into boiling Fehling's solution. The precipitated cuprous oxide would be dried and weighed, and would give directly the amount of sugar formed by the action of the enzyme. After obtaining a series of data in this way, a curve could be drawn, showing the amount of change of starch which had occurred in each unit of time. In the case of the action of invertase on cane sugar the investigation is still easier. Since the change from cane sugar to invert sugar is accompanied by a change in the rotatory power of the solution on polarised light, it is necessary only to put the mixture of enzyme and cane sugar into a polarimeter tube, which is kept at a constant temperature by means of a water jacket, and read off at intervals of a few minutes the change in the rotatory power of the solution. From this change can be easily calculated the percentage of cane sugar which has been converted into fructose and glucose.

In investigating the action of proteolytic enzymes, as *e.g.* that of trypsin on caseinogen, samples are taken at five-minute intervals and run into some substance such as trichloroacetic acid, which will precipitate all the unchanged protein, but will leave in solution the products of hydration of the protein. From the amount of nitrogen in the filtrate from the precipitate can be determined the total amount of protein which has undergone hydration in the sample under observation. A very convenient method is that employed by Henri and by Bayliss in the investigation of the kinetics of tryptic action, namely the determination of the conductivity of the solution. In the disintegration of the molecule caused by the action of the enzyme, there is a continuous increase in the conductivity of the solution, and this increase can be regarded as an index to the rate of change in the substances undergoing disintegration.

By such methods it has been found that, when the quantity of enzyme employed is very small in comparison with the *substrate* (the substance acted upon), the amount of change in a given time is proportional to the amount of enzyme present, and is (within limits) independent of the concentration of the substrate. This is well shown by the two following Tables representing the action of lactase upon lactose (E. F. Armstrong) :

PROPORTIONS HYDROLYSED IN 100 C.C. OF A 5 PER CENT.
SOLUTION OF LACTOSE

Solutions containing—	1·5 hours	20 hours	45 hours
1 c.c. lactase	0·15	2·2	3·9
10 c.c. „	1·6	23·3	38·6
20 c.c. „	3·2	45·8	—

AMOUNT OF SUGAR (LACTOSE) HYDROLYSED

Solutions containing—	24 hours		46 hours	
	Proportion	Weight	Proportion	Weight
10 per cent. lactose .	14.2	1.42	22.2	2.22
20 " " " .	7.0	1.40	10.9	2.18
30 " " " .	4.8	1.44	7.7	2.21

Moreover if we take only the earlier stages of the enzyme action, it is found that, with small proportions of enzyme, equal amounts of substrate are changed in successive intervals of time until about 10 per cent. has been hydrolysed. This is shown in the following Table:

2 PER CENT. LACTOSE WITH LACTASE

Time	Amount hydrolysed							
$\frac{1}{2}$ hour	.	.	.	.	.	.	.	3.2
$\frac{1}{2}$ "	.	.	.	.	.	.	.	6.4
1 "	.	.	.	.	.	.	.	9.6
2 hours	.	.	.	.	.	.	.	16.4
3 "	.	.	.	.	.	.	.	20.8

These results can be interpreted only by assuming that the first stage in the reaction is a combination of enzyme with substrate. It is only this compound which represents the active mass of the molecules, *i.e.* the molecules of substrate which are undergoing change. This compound, as soon as it is formed, takes up water and breaks down, setting free the hydrolysed substrate and the enzyme, which is at once ready to combine with a further portion of the substrate. In such a case the velocity of reaction must be directly proportional to the amount of enzyme, and the same absolute quantity of substance will continue to be changed in succeeding units of time. Supposing for instance we had at the bottom of a hill a load of bricks which had to be transferred to the top, and five men to effect the transference. The rate of transference would be directly proportional to the number of men employed; we could double the rate by doubling the men. Moreover the number of bricks carried in each unit of time would be the same. Five men would carry as many bricks in the second ten minutes as they would in the first, and so on. On the other hand, the velocity with which the transference was effected would be independent of the number—that is, the *concentration*—of the bricks at the bottom of the hill. The *active mass* of bricks could be regarded as that number carried at any moment by the transferring factor, namely the men. The equation of change would be $\phi = KC$, where C is the concentration of the enzyme. This concentration is always being renewed and kept constant by the breaking down of the intermediate product, so that the rate of change would be continuous throughout the experiment.

On the other hand when the amount of enzyme is relatively large, the rate of change, though at first very rapid, tends continuously to diminish. This is shown by the following Table representing the rates of change, during succeeding intervals of ten minutes, in a caseinogen solution to which a strong solution of trypsin had been added (Bayliss).

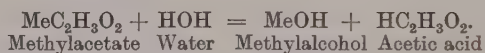
VELOCITY OF TRYPSIN REACTION

6 c.c. 8 per cent. Caseinogen + 2 c.c. $\frac{N}{10}$ AmOH + 2 c.c. 2 per cent. Trypsin at 39° C.

1st 10 minutes	.	.	.	.	.	.	.	K = 0.0079
2nd	"	.	.	.	.	.	.	0.0046
3rd	"	.	.	.	.	.	.	0.0032
4th	"	.	.	.	.	.	.	0.0022
5th	"	.	.	.	.	.	.	0.0016
6th	"	.	.	.	.	.	.	0.0009
&c.								&c.

The cause of this rapid diminution in the velocity of change is probably complex. One factor may be an auto-destruction of the enzyme, which is known to occur in watery solution. That this is not the only or even the chief factor involved is shown by the fact that, when the action of trypsin on caseinogen has apparently come to an end, it may be renewed by further dilution of the mixture or by removal of the end products of the action by dialysis. In this retardation of the later stages of enzyme action, the end products are concerned in some way or other, and the retardation can be augmented by adding to the digesting mixture the boiled end products of a previous digestion. The retarding effect of the end products resembles in many ways that observed in a whole series of reactions which are known as reversible.

As an example of such a reaction we may take the case of methyl acetate and water. When methyl acetate is mixed with water, it undergoes decomposition with the formation of methyl alcohol and acetic acid. On the other hand if acetic acid be mixed with alcohol, an interaction takes place with the formation of methyl acetate and water. These changes are represented by the equation:



Each of these changes has a certain velocity constant and, since they are in opposite directions, there must be some equilibrium point where no change will occur, and there will be a definite amount of all four substances present in the mixture, namely water, alcohol, ester and acid. This equilibrium point can be shifted by altering the amount of any of the four substances. Thus the interaction of methyl acetate and water can be diminished to any desired extent by adding to the mixture the products of the interaction, namely methyl alcohol and acetic acid.

There is evidence that some of the enzyme actions are reversible. Thus maltase acts on maltose with the formation of two molecules of glucose. If the maltase be added to a concentrated solution of glucose, we get a reverse effect, with the production of a disaccharide which has been designated as isomaltose or revertose. To this reverse action may be due a certain amount of the retardation observed in the action of trypsin on coagulable protein. A more important factor is probably the combination of the enzyme itself with the end products and the consequent removal of the enzyme from the sphere of action. Several facts speak for such a mode of explanation. Thus the action of lactase on milk sugar is not retarded by both its end products glucose and galactose but only by galactose. In the same way the action of invertase on cane sugar is retarded by the end product fructose but not at all by the other end product glucose.

So far therefore a study of the velocity of enzyme actions would lead us to suspect that the enzyme combines in the first place with the substrate, and that this combination is a necessary step in the alteration of the substrate. In the second place, the enzyme is taken up to a certain extent

by some or all of the end products, and this combination acts in opposition to the first combination, tending to remove the enzyme from the sphere of action and therefore to retard the whole reaction. Other facts can be adduced in favour of these conclusions. Thus it has been shown that invertase, which is destroyed when heated in watery solution at a temperature of 60°C ., can, if a large excess of its substrate cane sugar be present, be heated 25° higher without undergoing destruction. The same protective effect is observed in the case of trypsin. Trypsin in watery or weakly alkaline solutions undergoes rapid decomposition. At 37°C . it may lose 50 per cent. of its proteolytic power within half an hour. If on the other hand trypsin be mixed with a protein such as egg albumin or caseinogen or with the products of its own action, namely albumoses and peptones, it can be kept many hours without undergoing any considerable loss of power.

It has been found that, whereas maltase splits up all the α -glucosides, it has no power on the β -glucosides: that is to say, maltase will fit into a molecule of a certain configuration, but is powerless to affect a molecule which differs from the first only in its stereochemical structure. On the other hand emulsin, which breaks up β -glucosides, has no influence on α -glucosides. This specific affinity of the enzymes for optically active groups of bodies suggests that the enzyme itself may be optically active. We cannot of course isolate the enzyme and determine its optical behaviour; but that it is optically active is rendered probable both by these results and by those obtained by Dakin on lipase, the fat-splitting enzyme. He carried out his experiments on the esters of mandelic acid. Mandelic acid is optically inactive, but this optically inactive modification consists of a mixture of equal parts of dextro-rotatory and lævo-rotatory mandelic acid. The esters prepared from the optically inactive acids are themselves optically inactive. Dakin found that, when an optically inactive mandelic ester was acted upon by a lipase prepared from the liver, the final results of the action were also inactive; but if the reaction were interrupted at the half-way point, the mandelic acid which had been liberated was dextro-rotatory, while the remainder of the ester was lævo-rotatory. Thus the rate of hydrolysis of the dextro-component of the ester is greater than that of the lævo-component, a result which can be best explained by the assumptions (a) that the enzyme or a substance closely associated with it is a powerfully optically active substance; (b) that actual combination takes place between the enzyme and the ester undergoing hydrolysis. Since the additive compounds thus formed in the case of the dextro- and lævo-components of the ester would not be optical opposites, they would be decomposed with unequal velocity, and thus account for the liberation of the optically active mandelic acid.

Enzymes, which are all of a colloidal or semi-colloidal character, cannot be dealt with in the same way as the catalysts of definite chemical composition such as molybdic acid or nitric oxide. In many cases the substrate e.g. starch or protein is also colloidal, and the combination therefore falls into the class of combinations between colloids. In this we have an interaction between two substances in which the adsorption by the surfaces of the molecules of one or both substances plays an important part, though this adsorption is itself determined or modified by the chemical configuration of the molecules. The combination of enzymes with their substrates belongs therefore to that special class of interactions which we have discussed earlier under the name of *adsorption compounds*.

ENZYMES AS SYNTHETIC AGENTS

If maltase, obtained from yeast or from takadiastase (prepared from *Aspergillus oryzae*), be added to a solution of maltose, the latter is hydrolysed to glucose. The process of hydrolysis stops short of complete inversion at a point varying with the concentration of the sugar solution. Thus in a 10 per cent. solution of maltose, inversion proceeds until 98 per cent. of the

maltose is converted into glucose, whereas in a 40 per cent. solution the change stops short at 85 per cent. inversion. Croft Hill showed that if the maltase were added to a 40 per cent. solution of glucose, a change took place in the reverse direction, which proceeded until 85 per cent. of the glucose was left. The sugar formed, which is a disaccharide, is the stereoisomeric sugar, iso-maltose.

In the same way it has been found by Castle and Loewenhardt that the hydrolysis of esters by lipase is a reversible reaction, the action of lipase being simply to hasten the attainment of the equilibrium point between the four substances—ester (or neutral fat), water, fatty acid and alcohol. Wasteneys and Borsook have shown that native protein can be resynthesised from its hydrolysis products by the action of pepsin at a pH of 4.0 and particularly at a relatively high temperature, *e.g.* 70° C. Addition of protein delays the synthesis. A similar synthesis is effected by trypsin at pH 5.7.

If all enzyme actions are in this way reversible, a possibility is opened of regarding the synthetic processes occurring in the living cell, as well as the processes of disintegration, as determined by the action of enzymes. It must be noted that these effects are obtained with distinctness only when dealing with concentrated solutions. The degree of synthesis, which would be produced in the very dilute solutions of glucose &c. occurring in the animal cell, would therefore be infinitesimal. But if a mechanism were provided for the immediate separation of the synthetic product from the sphere of reaction, either by removing it to a different part of the cell or by building it up into some more complex body which was not acted on by the enzyme, the process of synthesis might go on indefinitely, and the infinitesimal quantities be summated to an appreciable amount.

Some experiments by Bertrand on fat synthesis have been interpreted as showing that the process of synthesis by enzymes is not the mere attainment of an equilibrium point in a reversible reaction. It has long been known that watery extracts of the fresh pancreas split neutral fats into the higher fatty acids and glycerol. This observer has shown that, if the pancreas be dried with alcohol and ether and powdered, addition of the dry powder to a mixture of the higher fatty acids and glycerol brings about a rapid synthesis of neutral fat. The process of synthesis is at once stopped by the addition of water. In this case either there are two enzymes present, one a synthesising the other a hydrolysing enzyme, differing in their conditions of activity, or there is one enzyme which may act either as a fat-splitting or fat-forming agent according to the conditions under which it is placed. In the latter case the effect of the addition of water would be simply to alter the equilibrium point of the mixture. It has been shown that in all reversible reactions the equilibrium position is the same from whichever side it be approached. The action of the enzyme is to hasten the attainment of equilibrium, the position of the latter being determined by the relative concentration of the reacting molecules.

TYPES OF CHEMICAL CHANGE

In spite of the enormous diversity of chemical reactions occurring in the body, they may be divided into a relatively small number of types. Nearly all the reactions are reversible. The chief types of chemical change are as follows:

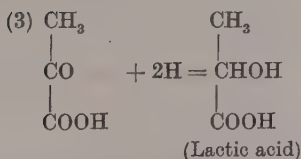
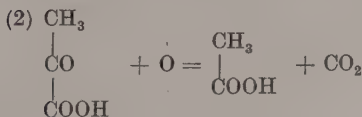
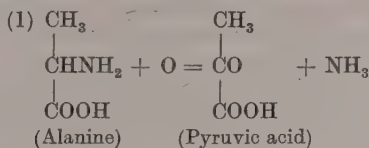
(1) **HYDROLYSIS.** In most cases this involves the taking up of water and a decomposition into smaller molecules. Thus the proteins are broken down in the intestine into their constituent amino-acids. The disaccharides such as maltose or lactose take up one molecule of water and give rise to two molecules of monosaccharide. The fats take up three molecules of water with the formation of fatty acid and glycerol. Hippuric acid is broken down into benzoic acid and glycine. The reverse change, that of dehydra-

tion, is also effected apparently with equal facility by the living cell, the hexoses losing water and being converted into a complex starch or glycogen molecule, while the amino-acids are built up first into polypeptides, and these again into the complex proteins of the cell. Besides the reactions in which there is a difference in the amount of free water on the two sides of the equation, it seems probable that hydrolysis and simultaneous dehydration at different parts of the molecule determine a number of chemical transformations, which at first sight seem to involve a simple splitting of the molecule. An example of such a process is afforded by the conversion of glucose into lactic acid described on p. 73.

(2) DEAMINATION. This process involves the splitting off from an amino-acid of an NH_2 group as ammonia. Many tissues of the body appear to have this power. In most cases the nature of the change in the remaining fatty moiety of the molecule has not yet been ascertained. If for instance to a mass of liver cells some amino-acid such as glycine, alanine or leucine be added, ammonia is set free in proportion to the amount of amino-acid added. This ammonia is therefore assumed to be derived from the amino-acid.

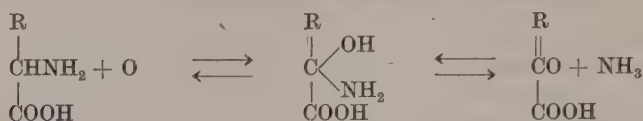
Work by Neubauer tends to show that deamination is accompanied in the first place by oxidation, so that the first intermediate product formed is an α -ketonic acid. A second atom of oxygen is then taken up and carbon dioxide is split off, with the production of the next lower acid of the series, or alternatively, by reduction it is converted to a hydroxy acid.

We may represent these changes as follows :



Is the reverse change ever effected in the animal body? If it were possible to replace the O in an α -ketonic acid by HNH_2 , it ought also to be possible to nourish an animal on a mixture of carbohydrates and ammonia, or at any rate by supplying him with a mixture of the appropriate hydroxy-acids or ketonic acids and ammonia. Until recently there was no evidence that the animal body is able to utilise nitrogen, except in organic combination as amino-acids or the complex aggregate of amino-acids known as proteins. In the plant it is probable that the formation of amino-acid occurs by a process the reverse of that which we have just been studying. Knoop has shown that the same reversed change may occur even in a mammal, and that here again the intermediate substance is an α -ketonic acid. On administering benzylpyruvic acid ($\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{COOH}$) to a dog, a certain amount of benzylalanine ($\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHNH}_2\cdot\text{COOH}$)

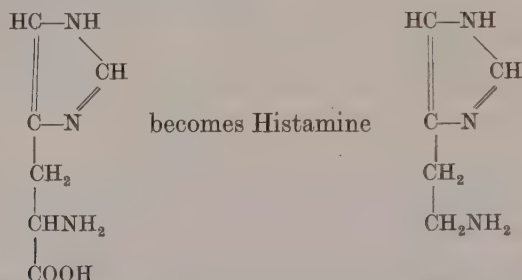
appeared in the urine. The first phase of the oxidative deamination of amino-acids is thus a reversible one and may be represented :



(3) DECARBOXYLATION. Many amino-acids when subjected to the action of bacteria lose a molecule of carbon dioxide and are converted into a corresponding amine.

For instance lysine, which is diamino-caproic acid, is converted into pentamethylene diamine or cadaverine.

and Histidine



In the same way ornithine derived from the breakdown of arginine is converted by putrefactive bacteria into tetra-methylene diamine or putrescine. Other examples of this process of decarboxylation are :

Isoamylamine $(\text{CH}_3)_2\text{CH}.\text{CH}_2.\text{CH}_2.\text{NH}_2$, from leucine.

β phenylethylamine $\text{C}_6\text{H}_5.\text{CH}_2.\text{CH}_2.\text{NH}_2$, from phenylalanine.

Para-hydroxyphenylethylamine $\text{HO}.\text{C}_6\text{H}_4.\text{CH}_2.\text{CH}_2.\text{NH}_2$, from tyrosine.

A similar process has been supposed to take place as a step in the successive oxidation of the carbon atoms in the long chain fatty acids or carbohydrates, but a thorough study of this process as it occurs in the higher animals is still wanting, and its very existence is indeed still hypothetical. In the case of the fats the oxidation takes place chiefly or entirely in the β position. The reverse reaction, namely the insertion of the group CO.O at the end of the long carbon chain, is not known. In the case of the fats the building up, like the oxidative breakdown, appears to occur by two carbon atoms at a time ; hence all the fatty acids met with in the body have an even number of carbon atoms in their chain.

It is worthy of note that all the changes which we have been considering --changes which not only account for the greater part of the chemical reactions of the living body, but may lead to the production of the most complex substances known--involve but little expenditure of energy. This is evident if we examine the heat evolved by the total combustion of 1 gramme molecule of the initial and final substances in a number of typical reactions. In the following Table these are given for the substances involved in typical instances of the three classes of chemical change that we have just been considering :

(1) HYDROLYSIS

Initial substance	Heat of combustion per gramme molecule	Final substance	Heat of combustion
Maltose	1350	2 Glucose	1354
Glucose	677	2 Lactic acid	659
Hippuric acid	1013	{ Glycine 235	1008
		{ Benzoic acid 773	

(2) DEAMINATION

Initial substance	Heat of combustion	Final substance	Heat of combustion
Alanine	389.2	Lactic acid	329.5
Leucine	855	Caproic acid	837
Aspartic acid	386	Succinic acid	354

(3) DECARBOXYLATION

Initial substance	Heat of combustion	Final substance	Heat of combustion
Alanine	389	Ethylamine	409
Leucine	855	Isoamylamine	867

(4) OXIDATION AND REDUCTION. The fourth class of chemical reactions differs from those just described in being attended with a very considerable energy change. This class involves the processes of oxidation and reduction. In almost every living cell, by far the largest amount of the energy available for the discharge of the functions of the cell is derived from the oxidation of the foodstuffs. If we take the final changes in the foodstuffs, the very large evolution of energy attending their oxidation is at once apparent. Thus in the conversion of glucose into CO_2 and water there is an evolution for each gramme molecule of 677 Calories. In the combustion of glycerol 397 Calories are evolved. In the oxidation of a fat such as trimyristin there are 6650 Calories evolved. The change does not in the living cell occur all at once, but the molecule is oxidised step by step. The energy thus liberated may be used as heat in warming the tissues in which the chemical changes occur. It may be converted into work, mechanical or osmotic, or it may be used in whole or in part for effecting other chemical reactions which involve absorption of energy.

Oxidation in the animal body is in most cases dependent on the presence of oxygen, derived as a rule from the external medium. There is no evidence that the body has the power of storing oxygen for subsequent use to any appreciable extent. It is usual to speak of oxidation not only in cases of absolute addition of oxygen to a molecule but also in cases where hydrogen is withdrawn from a molecule, and the latter change might occur in the absence of oxygen provided that there is some substance which can take up the liberated hydrogen. In the presence of water, as already mentioned, we may obtain coupled reactions representing simultaneous processes of oxidation and reduction. Thus benzaldehyde may be converted into benzoic acid and benzyl alcohol :

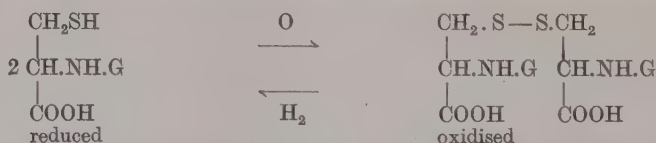


and the same change occurs with other aldehydes.

Most of the foodstuffs and the constituents of the organism which undergo oxidation in the body are comparatively stable substances with no affinity for free oxygen. The question arises as to the means available in the body for bringing the oxygen into such a state that it will combine with the substances which form the food and serve as the chief source of energy to the body. It has long been known that hydrogen peroxide is able to effect oxidative changes, which occur by stages similar to those observed in the animal body. Thus Dakin has shown that the series of fatty acids, under the action of hydrogen peroxide, undergo progressive oxidation in the β position, so that the carbon atoms are removed from the long chain of fatty acids two at a time. The action of hydrogen peroxide is much quickened by the presence of a trace of iron in the ferrous condition (Fenton's reaction): the iron thus acts as a catalyser. There is considerable evidence that this system, peroxide + catalyser, is actually reproduced in the living cells. According

to Bach and Chodat, many of the oxidations occurring in organisms are effected by the simultaneous action of an oxygenase and of a peroxidase. The peroxidase is an enzyme or catalyst. In some cases it may be manganese as in laccase, or iron as in Fenton's reaction. The oxygenase is an organic substance which is spontaneously oxidised by free oxygen to form a peroxide, either an organic peroxide or hydrogen peroxide. The peroxidase is able to produce active oxygen in presence of these peroxides, so that the mixture of oxygenase and peroxidase, which is called an aerobic oxidase, is able to carry out oxidations when free oxygen is present. The almost universal presence of a catalase in tissues may have as its object to destroy any excess of hydrogen peroxide which is produced in this way. Catalase breaks up hydrogen peroxide with the formation of water and molecular oxygen, so that it cannot function as a peroxidase, which splits off oxygen from hydrogen peroxide in the active condition.

We have seen that oxidation may imply either withdrawal of hydrogen or the addition of oxygen to a molecule. In the former case, if the process is to continue, there must be some substance present which can act as a hydrogen acceptor, taking up the hydrogen which has been set free by the reaction. On the other hand, since the oxygen of the air, blood and tissue fluids is in a free molecular condition, it must be activated by combining with some substance which acts as an oxygen acceptor and which can pass on the oxygen so combined to the body, which has to undergo continual oxidation. Thus we should expect processes both of oxidation and reduction to be continually occurring in the living tissues, though the final result will be one in which oxidation predominates. That both these processes occur is shown by the behaviour of methylene blue in contact with the tissues or with extracts of the tissues. If an extract of liver be made and some methylene blue added to it and the mixture be corked, the methylene blue rapidly undergoes reduction by taking up hydrogen and becomes colourless. On shaking the mixture with air, the colour is restored owing to the re-formation of methylene blue. In these processes of reduction and oxidation probably many different mechanisms are involved, according to the nature of the tissue and the nature of the substance *e.g.* fat, amino-acid or carbohydrate, which is undergoing oxidation. Considerable light has been thrown on one of these mechanisms by Hopkins' discovery of *glutathione*. This is a substance almost universally present in animal tissues. It is a dipeptide of cystein and glutamic acid. Although present in minute quantities, it plays an important part in the processes of oxidation and reduction which occur in the cells, since under suitable conditions it can function either as a hydrogen acceptor or as an oxygen acceptor, as seen from the following equation :



G stands for the glutamic acid part of the molecule, which is not directly concerned in these changes. In the reduced form this compound readily undergoes oxidation by air, when in neutral or slightly alkaline solution. It therefore acts as an oxygen acceptor, the oxygen being converted into hydrogen peroxide, as in an oxygenase. On the other hand, the oxidised or di-sulphide form is reduced by the reducing substance in tissues on the acid side of neutrality. Thus the rate of reduction of methylene blue by fresh tissues is retarded in acid solution by the presence of the disulphide

form, because this competes with the methylene blue for hydrogen; whereas in neutral or alkaline solutions the presence of the disulphide accelerates decolorisation of the blue, because as soon as some of it is destroyed it becomes autoxidised back again. Fresh chopped up muscular tissue respire, *i.e.* it takes up oxygen and gives off CO_2 . If it be thoroughly washed, this process of respiration comes to an end as well as its property of reducing methylene blue. The addition of glutathione to the washed muscle restores not only the respiration but also the power of reducing the dyestuff. Meyerhof has shown that, even if the muscle tissue has been heated to 100°C ., the addition of glutathione to it still restores the property of 'respiration' and of reducing methylene blue. Thus in addition to the mechanisms for oxidation and reduction, such as those described by Bach and Chodat and others, which are thermo-labile, there are present in the cell other systems such as the glutathione system, which can resist the temperature of boiling water. We have no light as yet on the mechanism of oxidation of lactic acid which plays so important a part in the activity of muscle. It seems that it is the unsaturated fatty acids, contained in the lecithin of the washed and heated muscle, and the proteins, which undergo oxidation in the presence of air and glutathione.

It must be remembered that in most cases the oxidative processes in the cell depend on the integrity of the structure of the cell, so that they are much diminished if the cell structure is destroyed by grinding. We are probably concerned here with surface effects occurring at the interfaces between different phases of the cell protoplasm and especially at the surfaces of the cell itself and of the nucleus. Similar effects of surface are familiar in non-living material. Thus certain amino-acids, especially cystein, are oxidised at room temperature to carbon dioxide and ammonia on shaking their solution with blood charcoal. This oxidation probably takes place at the surface of the charcoal particles, and it seems that here, as in the oxidase system already discussed, the presence of iron plays an important part. It is interesting to note that the oxidation of amino-acids by charcoal is inhibited, in a manner similar to the inhibition of oxidation in the living cell, by narcotics and by cyanides. Warburg suggests that narcotics act by being adsorbed on the surface and thus displacing the oxidisable substances, whereas cyanides probably act by inactivating the iron catalyst.

BOOK II
MUSCLE AND NERVE

CHAPTER XI

VOLUNTARY STRIATED MUSCLE

THE most striking features in the continual series of adaptations to the environment which make up the life of an individual are the movements carried out by contractions of the skeletal muscles. With the growth of the cerebral hemispheres, which determined the rise in the scale of animal life, the skeletal muscles become more and more the machinery of conscious reaction. The highest of the adaptations possessed by man are those involving the use of speech. A man's relation to his fellows and his value in the community are determined by these higher muscular adaptations. It is not therefore surprising that the organs of movement should have early

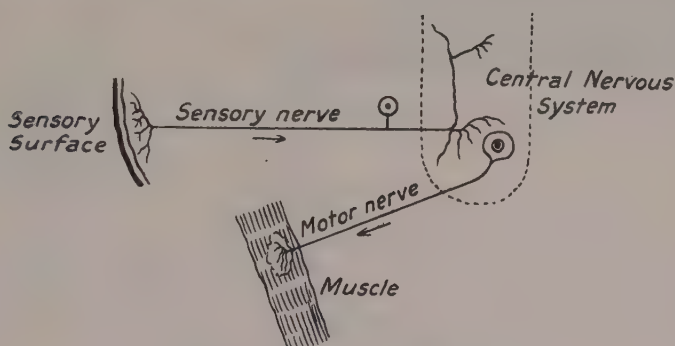


FIG. 34. Diagram of a Reflex Arc.

attracted the attention of physiologists and have been the object of numberless researches.

The movements of the muscles are normally carried out in response to changes aroused in the central nervous system by events occurring in the environment of the body. Every movement of an animal is thus in its most primitive form a reflex action, and involves changes in a peripheral sense organ, in an afferent nerve fibre, in the central nervous system, and in an efferent nerve fibre, before the actual process of contraction occurs in the muscle itself and gives rise to the resultant movement (Fig. 34). If we are to determine the nature of the changes involved in this reflex action, we must be able to study them as they progress along the different elements which make up the reflex arc. This analysis is facilitated by the fact that we are able to arouse a condition of activity in the different parts of the arc, even when isolated from one another. Thus we can excite any given reflex movement by suitable stimulation of the periphery of the body, or of the afferent nerve passing from the surface to the central nervous system. We can proceed further and cut the efferent nerve away from the central nervous system and still succeed in exciting a condition of activity in the efferent nerve or in its attached muscle. All parts of the reflex arc

possess the property of excitability, and we are thus able to arouse the activity of each part in turn, to study its conditions, its time relations, and the physical and chemical changes concomitant with the state of activity.

It will be convenient for our analysis to begin with the tissue whose reaction forms an end link in the reflex chain, namely the muscle, and to proceed from that to the consideration of the processes occurring in the conducting strand between central nervous system and muscle, namely the nerve fibre, postponing to a future chapter the treatment of the more complex processes associated with the central nervous system.

In the higher animals we may distinguish three varieties of muscle. All movements that require to be sharply and forcibly carried out are effected by means of striated muscular tissue and, as these movements are in nearly all cases under the control of the will, the muscles are generally spoken of as *voluntary*. Plain or *involuntary* muscles form sheets or closed tubes surrounding the hollow viscera. By their slow prolonged contractions they serve to maintain and regulate the flow of the contents of these

organs. Such fibres are found surrounding the blood vessels, the alimentary canal, the bladder, &c. Intermediate in properties as well as in structure between these two classes is the *heart muscle*. This like voluntary muscle is striated, but presents considerable variations both in structure and function from ordinary skeletal muscle. Many of its properties will be considered in treating of the physiology of the heart.

The properties of contractile tissues have been most fully investigated in the voluntary muscles, almost exclusively those of cold-blooded animals such as the

frog. The choice of skeletal muscles for this purpose is justified by the fact that a function is most easily investigated in the organs in which it is most highly developed. The selection of cold-blooded animals is guided by the fact that it is possible to isolate the muscle from the rest of the body and to keep it alive long enough to study its reactions during a considerable time. We shall therefore deal at length with the properties of the skeletal muscles, pointing out incidentally in what respects the heart muscle and involuntary muscle differ from the skeletal muscle.



FIG. 35. Muscular Fibre of a Mammal, examined fresh in serum, highly magnified. (SCHAFER.)

STRUCTURE OF VOLUNTARY MUSCLE

The voluntary or striated muscles form up to 50 per cent. by weight of the body and are known as the flesh or meat. Each muscle is embedded in a layer of connective tissue and is made up of an aggregation of muscular fibres, which are united into bundles by means of areolar connective tissue. The individual fibres vary much in length and may be as long as 4 or 5 cm. At each end of the muscle the fibres are firmly united to tough bundles of white fibres, which form the tendon of the muscle and are attached as a rule to bones. Running in the connective tissue framework of the muscle we find a number of blood vessels, capillaries and nerves.

On examination of a living muscle, each fibre is seen to consist of a series of alternate light and dark striæ, arranged at right angles to its long axis and enclosed in a structureless sheath—the sarcolemma. Lying under the sarcolemma are a number of oval nuclei embedded in a small amount of granular protoplasm. Each band may be considered to be made up of a number of prisms (sarcomeres) side by side, with interstitial substance (sarcoplasm) between them. The muscle prisms of adjacent discs are connected to form long columns (primitive fibrillæ or sarcostyles). Each muscle prism is more transparent at the two ends than in the middle, thus

giving rise to the appearance of light and dark striæ. In the middle of the light band is a line or row of dots (often appearing double) called Krause's membrane.

The development of this regular cross and longitudinal striation is closely connected with the evolution and specialisation of the muscular function, *i.e.* contraction. Contractility is among others a function of all undifferentiated protoplasm. Undifferentiated cells, such as the amoeba, can effect only slow and weak contractions. Directly a specialisation of function is necessary and some cell or part of a cell has to contract rapidly in response to some stimulus from within or without, we find a differentiation both of form and of internal structure. In many cases, as in the developing muscle of the embryo or the adult muscles of many invertebrates, this differentiation affects only part of the cell, so that, while one part presents the ordinary granular appearance, the other half is finely and longitudinally striated, the striation being apparently due to the development of special contractile fibrillæ. In the slowly contracting unstriated muscle of the vertebrate intestine, the longitudinal striation is with difficulty made out, but as the muscle rises in the scale of efficiency, the longitudinal striation becomes more apparent; and in the striated muscle of vertebrates, and still more in the wonderful wing-muscles of insects which can perform three hundred complete contractions in a second, the longitudinal is associated with and often apparently subordinated to a transverse striation, due to the regular segmentation of the contractile fibrillæ or *sarcostyles*. Every muscular fibre which presents any trace of histological differentiation may be said to consist of contractile fibrillæ (*sarcostyles*), each composed of a series of con-

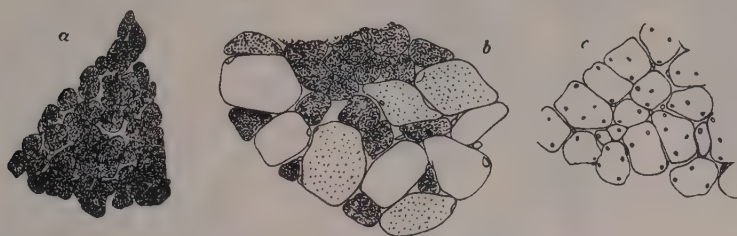


FIG. 36. Transverse sections of the Pectoral Muscles of *a*, the Falcon, *b*, the Goose, and *c*, the domestic Fowl. It will be noticed that the relative amount of granular or red fibres present varies directly as the bird's power of sustained flight. (After KNOLL.)

tractile elements (*sarcous elements* or *sarcomeres*) and embedded in a granular material known as *sarcoplasm*. The great divergence in the aspect of muscular fibres from different parts of the animal kingdom is largely conditioned by the varying relations, spatial and quantitative, of the sarcoplasm to the sarcostyles. Thus in the higher vertebrates, two types of voluntary muscular fibre are distinguished, according to the amount of sarcoplasm they contain: one rich in sarcoplasm, more granular in cross section and generally containing hæmoglobin; the other poor in sarcoplasm, clear in cross section and containing no hæmoglobin. From the fact that the granular fibres are found chiefly in those muscles which have to carry out long-continued and powerful contractions, it seems reasonable to regard the interstitial sarcoplasm as the local food-supply of the active sarcostyles, although some authors have endowed the sarcoplasm with a contractile power of its own, differing only by its extremely prolonged character from the quick twitch of the sarcostyles. The connection between structure and activity of the muscle fibres is well shown by Fig. 36.

In some animals, such as the rabbit, we find muscles consisting almost entirely of one or other of these varieties; but in most animals (amongst which we may reckon frog and man) the two varieties occur together in one muscle, so that what we have to say about the properties of voluntary muscle, which rests nearly entirely on experiments with frog's muscle, really has reference to a muscle containing both red and white fibres.

Since the sarcous element represents the contractile unit of the muscle, a knowledge of its intimate structure should be of great importance for the theory of muscular contraction. Unfortunately however we are here at the limits of the demonstrably visible. It becomes difficult to determine how far the appearances observed under the microscope are due to actual structural differences or are produced by the unequal diffraction of light by the various elements of the muscle fibre. All observers are agreed that the essential contractile element is the row of sarcous elements forming the muscle fibril or

sarcostyle. Schafer, working on the highly differentiated wing-muscle of the wasp, concludes that each sarcostyle is divided by Krause's membranes (the lines in the middle of each light stripe) into sarcomeres. Each sarcomere contains a darker substance near the centre divided into two parts by Hensen's disc. At each end of the sarcomere the contents are clear and hyaline. In the act of contraction, the clear material flows, according to Schafer, into tubular pores in the central dark material. Most histologists

agree in assigning to the middle part of the sarcoous element (the sarcomere) a denser structure than to the two ends. According to MacDougall however the lighter appearance at each end of the sarcomere is an optical illusion. He regards the sarcoous element as a cylindrical bag with homogeneous contents, crossed only by one or three delicate transverse membranes, of which Krause's is the more rigid. Tiegs considers that the membrane of Krause does not form simple transverse partitions across the fibril, but runs in a spiral form along its whole length as a continuous structure, between the turns of which the sarcomeres are placed.

When a muscle fibre, killed by osmic acid or alcohol, is examined under the microscope

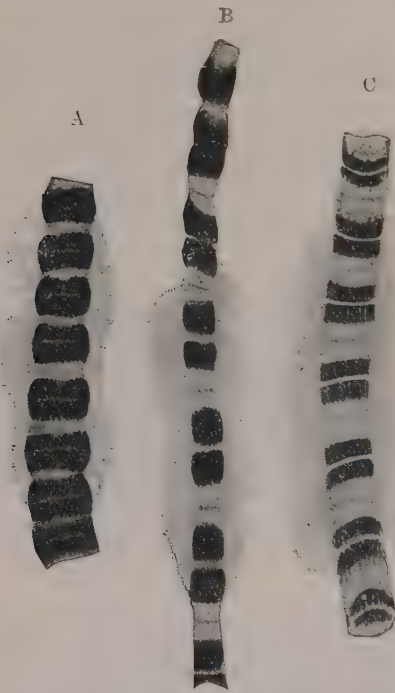


FIG. 37. Fibrils of the Wing-Muscles of a Wasp, prepared by Rollet's method. Highly magnified. (SCHAFFER.)

A, a contracted fibril. B, a stretched fibril, with its sarcoous elements separated at the line of Hensen. C, an uncontracted fibril, showing the porous structure of the sarcoous elements.

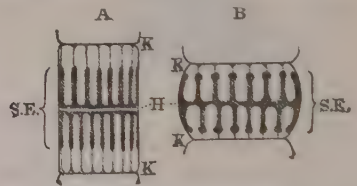


FIG. 38. Diagram of a Sarcomere in a moderately extended condition, A, and in a contracted condition, B: K, K, membranes of Krause; H, line or plane of Hensen; S.E., periferous sarcoous elements. (SCHAFFER.)

by polarised light, it is seen to be made up of alternate bands of singly and doubly refracting material. The doubly refracting (*anisotropic*) substance corresponds to the dark band, and the singly refracting (*isotropic*) to the light band. If the living fibre be examined in the same way, it is found that nearly the whole of it is doubly refracting, the singly refracting substance appearing only as a meshwork with long parallel meshes corresponding to the muscle prisms. In short, in a living fibre the muscle prisms are anisotropic, the sarcoplasm isotropic.

When a muscle fibre contracts, there is an apparent reversal of the situations of the light and dark stripes, owing to the fact that the interstitial sarcoplasm is squeezed out from between the bulging sarcomeres, and accumulates on each side of the membranes of Krause. The accumulation of sarcoplasm in this situation makes the previously light striæ appear dark, and the dark striæ by contrast lighter than they were before. That there is no true reversal of the striæ is shown by examining the muscle by polarised light, the two substances, isotropic and anisotropic, retaining their relative positions.

Every skeletal muscle is connected with the central nervous system by nerve fibres, some conveying impressions from the muscle to the centre, some being sympathetic fibres of unknown function, the others acting as the path of the motor impulses from the centre to the muscle. These last—the

motor nerves—terminate in the muscle fibre itself by means of a special end organ—the motor end plate. The neurilemma of the nerve fibre becomes continuous with the sarcolemma, the medullary sheath ends suddenly, while the axis cylinder ramifies in a mass of undifferentiated protoplasm, containing nuclei and lying in contact with the contractile substance of the muscle immediately under the sarcolemma (Fig. 39). This mass of protoplasm is known as the 'sole plate.' It is not marked in all animals. Thus in the frog the axis cylinder ends in a series of branches at right angles to one another, distributed over a considerable length of the muscle fibre. The sole plate in

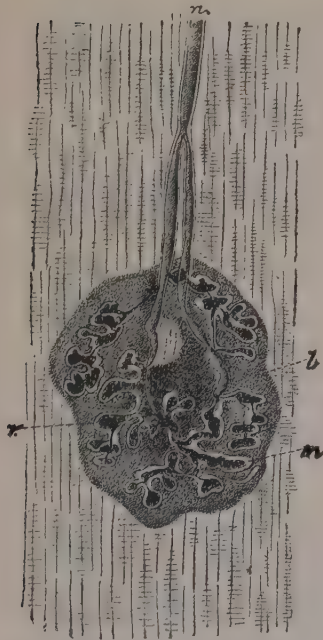


FIG. 39. Motor End Organ of a Lizard, gold preparation. (KÜHNE.)

n, nerve fibre dividing as it approaches the end organ; *r*, ramification of axis cylinder upon *b*, granular bed or sole of the end organ; *m*, clear substance surrounding the ramifications of the axis cylinder.

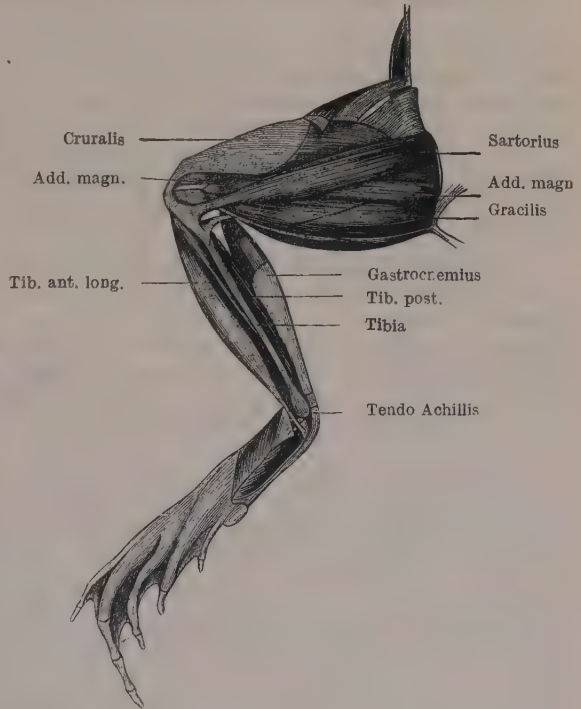


FIG. 40. Muscles of Hinder Extremity of Frog. (After ECKER.)

this case seems to be limited to scattered nuclei lying in close contact with the terminal branches of the nerve fibre. So far as we can tell at present, the ultimate ramifications of the axis cylinder end freely and do not enter into organic connection with the contractile substance itself.

Most of our knowledge on the subject of muscle has been derived from the study of the gastrocnemius and sartorius muscles of the frog. The position of these muscles is shown in the accompanying diagram (Fig. 40). The gastrocnemius with the attached sciatic nerve, is most frequently employed as a nerve-muscle preparation. On account of a penniform arrangement of the muscular fibres, the gastrocnemius can be employed only when the contraction of the muscle as a whole is the object of investigation. The effective cross area of the fibres is much greater than the actual cross section of the muscle so that, while the actual shortening of the gastrocnemius is but small, its strength of contraction is considerable.

The sartorius muscle is of especial value on account of the regularity with which its fibres are disposed. When a greater mass of approximately parallel fibres is necessary, recourse may be had to a preparation consisting of the gracilis and semimembranosus muscles together. This latter muscle lies dorsally to the gracilis muscle which is shown in the illustration.

Other muscles in the frog used for particular purposes are the mylohyoid and the dorsocutaneous muscles. The mylohyoid muscle of the frog, which lies on the ventral surface of the tongue, has the advantage that its fibres lie in close contact with a lymph space occupying the centre of the tongue. If any drug be injected into this lymph space it acts with extreme rapidity on the muscle fibres, so that the tongue preparation of the frog is a useful one for the study of the action of different substances on muscle fibres.

CHEMICAL COMPOSITION OF VOLUNTARY MUSCLE

The contents of the fibres are semi-fluid and can be expressed from the finely divided muscle as a viscous fluid known as muscle plasma. As in all cellular tissues, proteins form its chief chemical constituents.

Muscle plasma is obtained in the following way. The living muscle of frogs is frozen, minced with ice-cold knives and pounded in a mortar with four times its weight of snow containing 0.6 p.c. of common salt. The mixture is then thrown on to a filter kept at 0° C. when an opalescent fluid filters through.

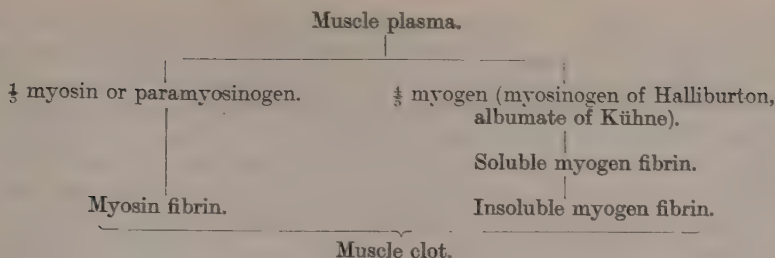
If the temperature of the muscle plasma be allowed to rise, clotting takes place, the clot later on contracting and squeezing out a serum. The muscle plasma is neutral or slightly alkaline. When coagulation takes place it becomes distinctly acid, and this acidity is due to the formation of sarcolactic acid in the process. Arguing chiefly from analogy with the blood plasma, the muscle plasma has been said to contain a body, *myosinogen*, which is converted when clotting takes place into *myosin*.

The exact nature of the proteins in muscle plasma, as well as of the protein constituent of the clot which we have called myosin, is still a subject of debate. Kühne, to whom we owe our first acquaintance with muscle plasma, described the clot as consisting of myosin, a globulin soluble in 5 per cent. solutions of neutral salts such as NaCl or MgSO₄, precipitated by complete saturation with MgSO₄, and coagulated on heating to 56° C. In the muscle serum, obtained after separation of the clot, he found three proteins, one coagulating at 45° C., one he called an albumate (*i.e.* a derived albumin or metaprotein), and the third coagulating about 75° C. and apparently identical with serum albumin. Halliburton extended these researches to the muscles of warm-blooded animals. He described four proteins as existing in muscle plasma, of which two, paramyosinogen and myosinogen, gave rise to the clot of myosin.

In no case however is it possible entirely to dissolve up the clot when once formed, and it seems that the so-called solution in dilute salt solutions was merely an extraction of still soluble protein in the meshes of the clot. Von Fürth has shown that, if the muscles of a mammal are washed free of adherent lymph and blood, the plasma obtained by extraction with normal salt solution contains only two proteins. These proteins are extremely unstable and are gradually transformed on standing into insoluble protein, giving rise to a precipitate in dilute solutions or forming a jelly-like clot in strong solutions. The properties of these proteins may be summarised as follows:

(1) Myosin (paramyosinogen of Halliburton). A globulin, coagulating at about 47°–50° C., precipitated by half saturation with ammonium sulphate or on dialysis; transformed slowly in solution, rapidly on precipitation, into an insoluble protein, myosin fibrin.

(2) Myogen (myosinogen of Halliburton). A protein allied to the albumins in that it is not precipitated by dialysis. Coagulates on heating at 55°–60° C. It changes slowly into an insoluble protein, myogen fibrin, but *passes through an intermediate soluble stage* called soluble myogen fibrin. This latter body coagulates on heating to 40° C., being instantly converted at this temperature into insoluble myogen fibrin. It does not seem that any enzyme action is associated with these changes which we may represent by the following schema:



Soluble myogen fibrin, which in mammalian muscle plasma forms only on standing, exists apparently preformed in frog's muscle. Hence the instantaneous clotting of frog's muscle plasma on warming to 40° C.

The residue left after the expression of the muscle plasma consists chiefly of connective tissue, sarcolemma and nuclei, and as such contains collagen, mucin, nuclein and adherent traces of the proteins of the muscle plasma itself.

The muscle serum contains the greater part of the soluble constituents of muscle.

OTHER CONSTITUENTS OF MUSCLE. A number of other substances are found in muscle in small quantities, those which are soluble being mostly in the muscle serum. It will suffice here to enumerate the chief of these:—

(a) *Colouring Matter.* All red muscles contain a considerable amount of hæmoglobin. A special muscle pigment allied to hæmochromogen was described by MacMunn as myohæmatin. It is now recognised as one of the cytochromes.

(b) *Nitrogenous Extractives.* Of these, the most important is creatine ($C_4H_9N_3O_2$) of which 0.2 to 0.3 per cent. may be found in muscle. It is present in combination with phosphoric acid to form the compound which has been called "phosphagen" by Eggleton. Its significance will be the subject of consideration later. Carnosine, which was shown by Barger and Tutin to be β -alanyl-histidine, is present to the extent of about 0.3 per cent. Its significance is unknown. Other nitrogenous bodies occurring in smaller quantities are hypoxanthine, xanthine and traces of urea and amino-acids.

(c) *Non-nitrogenous Constituents.*

Fats in variable amount and *lecithin*.

Glycogen. This substance is invariably found in healthy muscle. Fresh skeletal muscle contains about 1 per cent. In the embryo the muscles may contain many times this quantity of glycogen.

Glucose is present in fresh muscle in minimal quantities, about 0.01 per cent.

Hexose phosphates as monophosphate and diphosphate are also present.

When muscle is allowed to stand, especially in a warm place, the glycogen undergoes partial conversion into glucose, so that the latter increases at the expense of the former.

Inositol ($C_6H_{12}O_6 \cdot 2H_2O$) or 'muscle sugar' occurs in minute traces in muscle. It does not belong to the group of carbohydrates at all, being a hexahydroxybenzene. It is nonfermentable and does not rotate polarised light nor does it reduce Fehling's solution. Its significance is quite unknown.

(d) *Inorganic Constituents.* Muscle contains about 75 per cent. of water. Ash forms 1 to 1.5 per cent. and consists chiefly of potassium and phosphoric acid, with traces of calcium, magnesium, chlorine and iron. Most, if not all, the phosphoric acid is present in organic combination, chiefly as phosphagen, hexose phosphates and lecithin. It has recently been claimed that pyrophosphates also occur in muscle.

RIGOR MORTIS

All muscles after removal from the body, or if left in the body after general death, lose after a time their irritability, and this loss is succeeded by the phenomenon known as *rigor mortis*. The muscle, which was previously flaccid, contracts, though the shortening is not very powerful and

can be prevented by a moderate load on the muscle. Whereas the living muscle is translucent, supple and extensible, it becomes in the process of rigor opaque, rigid and inextensible. The rate of onset of rigor is greatly accelerated by warmth, or by treating the muscles with solutions of caffeine, arsenates or chloroform vapour. When rigor has been established, the reaction of the muscle is usually found to have changed from a slightly alkaline to a distinctly acid one, due to the presence of sarcolactic acid. From this condition of rigor there is no recovery of contractility, though the muscle softens before putrefaction sets in. There can be no doubt that the change in consistence of the muscle and probably also its shortening in rigor are due to changes in the muscle proteins. Both conditions can be imitated by heating the muscle. It seems likely however that the main contraction, at all events that which comes on spontaneously after death or immediately on warming the muscle to 45° C., has another component. In the coagulation of the separated muscle proteins there is no formation of sarcolactic acid, whereas the formation of this substance has often been held to bear an important relation to the occurrence of rigor. Thus after severe muscular fatigue, as in hunted animals, where there has already been a considerable formation of the waste products of muscular contraction, rigidity may come on almost immediately after death. If a thin living muscle be plunged into boiling water, it undergoes instant coagulation but *no chemical change*. The reaction of the scalded muscle, like that of fresh muscle, is slightly alkaline to litmus. No sarcolactic acid is produced. On the other hand, in surviving muscle, after the cessation of the circulation, there is a steady formation of lactic acid which accumulates in the muscle. It is tempting to suppose that the actual coagulation of the muscle proteins occurring in rigor is largely, if not entirely, determined by the increasing acidity of the muscle thereby produced.

Recent investigations suggest however that another factor which plays a part in determining the onset of *rigor mortis* is the disappearance of glycogen from the muscle. As the glycogen is converted into lactic acid it usually follows that the reaction of the muscle does become acid by the time the glycogen has vanished, but in certain special cases, *e.g.* after death from insulin convulsions, rigor sets in when all the glycogen has disappeared although the reaction of the muscles may still be alkaline.

THE PRODUCTION OF LACTIC ACID IN SURVIVING MUSCLE

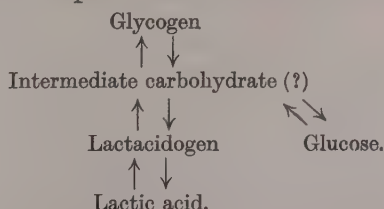
The lactic acid formed in muscle (sarcolactic acid) is a physical isomer of the lactic acid formed in the fermentation or souring of milk. They both have the formula $\text{CH}_3\text{CH}(\text{OH})\text{COOH}$, *i.e.* they are ethylidene lactic acids. The lactic acid of fermentation is optically inactive; sarcolactic acid rotates polarised light to the right; while a third isomer which is *laevo*-rotatory is produced by the action of various bacilli and vibrios on cane sugar. The sarcolactic acid can be extracted from the muscle by means of alcohol.

It was pointed out by Fletcher and Hopkins that most of the methods previously used for the extraction of lactic acid from muscle caused the formation of lactic acid in this tissue. To obviate this difficulty, they adopted the precaution of cooling the muscles before cutting them out of the body and then dropping them into alcohol cooled to 0° C. While in this ice-cold alcohol they were finely divided with scissors and then pounded up in a cooled mortar. In this way the tissue was destroyed at a temperature which did not allow of the changes responsible in surviving muscle for the production of lactic acid. It is generally separated in the form of the zinc sarcolactate, by boiling its partially purified solution with zinc carbonate.

Fletcher and Hopkins, using the precautions described above, showed that fresh muscle contains only minimal amounts of lactic acid, the quantity being smaller the greater the care that is taken to avoid injury to the muscle and to keep its temperature low until sufficient time has elapsed for its vital chemical processes to be destroyed by the action of the cold alcohol.

If the muscle be left in the body after the death of the animal or be excised, a steady formation of lactic acid takes place, which is more rapid in the first few hours after death, but continues until the muscle passes into rigor. With the complete onset of rigor, frog's muscles are found to contain about 0.4 per cent. lactic acid. After this time the amount does not increase. The onset of rigor and the rate of production of lactic acid are quickened if the muscle be kept warm. It is interesting to note that the amount of lactic acid found in rigid muscle is almost invariable whatever the previous history of the muscle. Thus, if the muscle be finely minced and then extracted with cold alcohol, it is found to contain about 0.2 per cent. lactic acid. If however it be allowed to stand after mincing, there is a slow production of lactic acid up to the maximum 0.4 per cent. Again, a muscle which has been tetanised to exhaustion contains about 0.2 per cent. lactic acid. When allowed to undergo rigor, the amount rises to about 0.4 per cent. This limitation depends on the fact that the accumulation of lactic acid inhibits its further formation. If care be taken to remove the lactic acid as it is formed by immersing the muscles in weak alkaline solutions, much greater amounts may be obtained. Meyerhof found that in muscles immersed in 2.4 per cent. Na_2HPO_4 through which hydrogen was passed to remove oxygen, the whole of the glycogen disappeared, and as much as 0.8 to 1.2 per cent. lactic acid was obtained.

Source of the Lactic Acid. The total disappearance of glycogen in this experiment points to this substance as the precursor of the lactic acid. Moreover the amount of lactic acid obtained in various muscles depends on the amount of glycogen already present, and is less after prolonged starvation and deprivation of carbohydrates. The change requires the presence of phosphates, and according to Embden takes place through an intermediate stage of hexosephosphoric acid which he speaks of as 'lactacidogen.' (It is interesting to note that in the fermentation of sugar by yeast, an intermediate formation of hexosephosphoric acid is an essential part of the process.) Glucose may also take part in the formation of lactic acid. The following schema represents the changes involved. It must be remembered that (as we shall see in dealing with the changes accompanying activity) in the living muscle all these steps are reversible.



It has long been known that the onset of rigor is associated with an evolution of carbonic acid by the muscle. Fletcher has shown that this increased output of carbonic acid by a surviving muscle is due simply to the driving off of this gas from the bicarbonates in the muscle as a result of the production of lactic acid. The lactic acid found in the surviving muscle reacts with the muscle proteins, deionising them; and it may be this effect rather than coagulation proper that is responsible for the shortening in rigor mortis, as well as in the contracture of fatigued muscle. Von Fürth suggests that the coagulation comes on much later and is the cause not of rigor but of the disappearance of rigor.

HEAT PRODUCTION IN RIGOR. When rigor occurs naturally or is brought on by chloroform vapour, there is an evolution of heat amounting to about 1.7 calories per gramme of frog's muscle. If the muscle be

stimulated to exhaustion, about 0.9 calorie per gramme is evolved. If then it be thrown into rigor, there is a further evolution of heat of about 0.8 calorie (A. V. Hill and Peters). There is thus a direct relation between the amount of lactic acid produced and the heat evolved under these conditions. The significance of this relation we shall discuss in dealing with the chemical and energy changes accompanying muscular contraction.

EXCITATION OF MUSCLE AND OTHER TISSUES

In order to avoid subsequent repetitions, we shall now consider the excitation of muscle, and at the same time give a general account of the excitability of other tissues, such as nerve.

A muscle may be caused to contract in various ways. Normally it contracts only in response to impulses starting in the central nervous system and transmitted down the nerves. But contraction may be artificially excited in various ways in a muscle removed from the body. If we make a nerve-muscle preparation (*i.e.* a muscle with as long a piece of its nerve as possible attached to it), such as the gastrocnemius of the frog with the sciatic nerve, we find we can cause contraction by various forms of stimuli—mechanical, thermal, or electrical—applied to the muscle or the nerve (direct and indirect stimulation). Thus the muscle responds with a twitch if we pass an induction shock through it or its nerve, or pinch either with a pair of forceps. Or we may use chemical stimuli, and cause contraction by the application of strong glycerin or salt solution to the nerve.



FIG. 41. The Ramification of the Nerve Fibres within the Sartorius Muscle of the Frog, showing the freedom of the lower portion of the muscle from nerve fibres. (KÜHNE.)

These experiments do not prove conclusively that muscle itself is irritable. It might be urged that, when we pinched or burnt the muscle, we stimulated, not the muscle substance itself but the terminal ramifications of the nerve in the muscle, and that these in their turn incited the muscle to contract. But the independent excitability of muscle is shown clearly in the classical experiment by Claude Bernard.

A frog, whose brain has been previously destroyed, is pinned on a board, and the sciatic nerves on each side exposed. A ligature is then passed round the right thigh underneath the nerve, and tied tightly so as effectually to close all the blood vessels supplying the limbs, without interfering with the blood supply to the nerve. Two drops of a 1 per cent. solution of curare are then injected into the dorsal lymph sac. After the lapse of a quarter of an hour it is found that the strongest stimuli may be applied to the left sciatic nerve without causing any contraction of the muscles it supplies. On the right side, stimulation of the nerve is as efficacious as before. Both gastrocnemii respond readily to direct stimulation, showing that the muscles are not affected by the drug. Since both sciatic nerves have been exposed to the influence of the curare, the difference on the two sides cannot be due to any deleterious effect on them by the curare. We have also excluded the muscles themselves. So we must conclude that the curare paralyses the muscles by preventing the excitatory process from passing over from the nerve to the muscle. This experiment teaches us that muscle can be excited to contract by direct stimulation, even when the passage of impulses from the nerves is prevented.

The same fact may be demonstrated in a different way by means of chemical stimuli. It is found that whereas strong glycerin excites nerve fibres, it is without effect on muscle fibres, while on the other hand weak ammonia is a strong excitant for muscle but is without effect on nerve. If the frog's sartorius be dissected out and the lower end dipped in glycerin, no twitch is produced. On snipping off the lower third of the muscle and then immersing the cut end in glycerin, a twitch at once occurs. The lower end contains no nerve fibres (Fig. 41), and it is only when a section containing nerve fibres is exposed to the action of glycerin that contraction takes place. On the other hand mere exposure of muscle to the vapour of dilute ammonia causes contraction (and

subsequent death), although the nerve to the muscle can be immersed in the solution without any excitation being produced.

Of all the different stimuli capable of exciting muscular contraction, the electrical is that most frequently employed. It is easy, using this form, to graduate accurately the intensity and duration of the stimulus. At the same time the stimulus may be applied many times to any point on the muscle or nerve without killing the part stimulated, whereas with other forms of stimulus it is difficult to obtain excitatory effects without injuring to a greater or less extent the part stimulated.

THE ELECTRICAL STIMULATION AND EXCITABILITY OF MUSCLE AND NERVE

The two commonest forms of electrical stimuli employed are (1) the make and break of a constant current, (2) the induction currents of high intensity and short duration obtained from an induction coil.

(1) CONSTANT (or Galvanic) CURRENT.

As a source of constant current a Daniell's cell is generally employed. This consists of an outer pot containing a saturated solution of copper sulphate, in which is immersed a copper cylinder. To the cylinder at the top a binding screw is attached, by which the connection of the copper with a wire terminal is effected.

Within the copper cylinder is a second pot of porous clay, filled with dilute sulphuric acid, in which is immersed a rod of amalgamated zinc. The current flows (in the cell) from zinc to copper, and if the binding screws of the two elements are connected by a wire, the current flows in the wire (outer circuit) from copper to zinc, thus completing

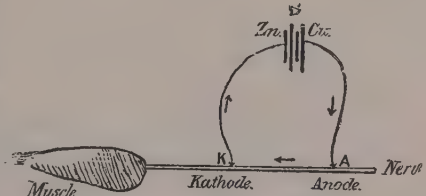


FIG. 42.

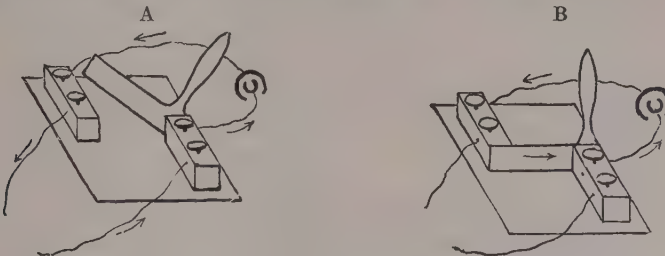


FIG. 43. Du Bois Key, short-circuit open.

Du Bois Key, short-circuit closed.

the circuit. Since in the outer circuit the current flows from copper to zinc, the terminal attached to the copper is called the positive *pole*, and that to the zinc the negative pole. When the current is required to be very constant, the zinc may be immersed in a saturated solution of zinc sulphate instead of dilute sulphuric acid. A Daniell's cell, though very constant, gives only a small current, owing to its small electromotive force and high internal resistance.

When a stronger current is required it is better to use an accumulator. In this, when charged, the two elements are lead and lead oxide, PbO_2 . It has the advantage that it may be used over and over again, being recharged through a resistance from the electrical mains when it has run down.

Another useful type of cell is the Leclanché cell. This consists of a glass jar containing a solution of sal ammoniac. Into this dips an amalgamated rod of zinc, which is the positive element. A piece of gas carbon forms the negative element. This is surrounded by peroxide of manganese (MnO_2) which is kept in contact with the surface of the carbon by being placed in a porous pot. The E.M.F. of one Leclanché cell is 1.4 volts in the external circuit. The wire attached to the carbon is the *positive pole*, that to the zinc the *negative pole*. Dry cells are usually Leclanché cells, in which the solution of sal ammoniac is prevented from spilling by absorption with sawdust or plaster of Paris.

If the poles of a Daniell's cell be connected by wires with a nerve or muscle of a nerve-muscle preparation (as in Fig. 42), the current will flow from copper to the nerve

at A, and along the nerve from A to K. At K the current will leave the nerve to flow to the zinc of the battery, so completing the circuit. The point at which the current enters the nerve (*i.e.* the point of the nerve connected with the positive pole of the battery) is called the *anode*, and the point at which the current leaves the nerve is called the *cathode*. The wires by which the current is conducted to and from the nerve are called the *electrodes*. As electrodes we generally employ two platinum wires mounted together on a piece of vulcanite.

For the purpose of making or breaking the current at will, various forms of keys are employed. Du Bois Reymond's key consists of two pieces of brass, each of which has two binding screws for the attachment of wires. These are connected by a third piece or bridge, which is jointed to one of the two side bits, so that it may be raised or lowered at pleasure (*v.* Fig. 43). It may be used either as a simple make-and-break key or, more usually, as a short-circuiting key. In the first case one brass bank is attached to one terminal, the other to the other terminal. If the bridge be now lowered, the connection is made and the current passes. If the bridge be raised, the current is broken.

Fig. 43 A and B shows the way in which the key is arranged for short circuiting. It will be seen that four wires are attached to the key; two going to the battery, and two (we may suppose) going to a nerve. When the bridge is down, as in Fig. 43 B, the current from the cell on coming to the key has a choice of two routes. It may either go through the brass bridge or through the other wires and nerve. The resistance of the nerve however is about 100,000 ohms, whereas that of the bridge is not the thousandth part of an ohm. When a current divides, the amount of current that goes along any branch is inversely proportional to the resistance. Here the resistance in the nerve circuit is practically infinite compared with that in the brass bridge, and so all the current goes through the bridge and none through the nerve. We say then that the current is *short circuited*.

It is often necessary to reverse the direction of a current through a nerve-muscle preparation or a galvanometer in the course of an experiment. For this purpose Pohl's reverser may be used. It consists of a slab of ebonite or paraffin or other insulating material, in which are six small holes filled with mercury. A binding screw is in connection with the mercury in each of these holes. Two cross wires (not in contact with one another) join two sets of pools together, as shown in Fig. 44. A cradle consisting of two wires joined by an insulating handle carries two arcs of wire by which the pools at *a* and *b* may be put into connection with either *x* and *y*, or the corresponding pools on the opposite side. It will be seen that with the cradle tipped to one side, as in Fig. 44 A, the current from the battery enters the reverser at *a*; this proceeds up the wire of the cradle, down towards the right, then along the cross-wire to the pool at *x*. *x* is therefore the anode, and *y* the cathode. In Fig. 44 B the cradle has been swung over to the other side. Here the cross wires are not used at all by the current, which passes from *a* up the sides and down the curved wire to *y*. In this case *y* is now the anode and *x* the cathode, and the direction of the current through the circuit connected with *x* and *y* is reversed. By taking out the cross wires, Pohl's reverser may be used as a simple switch, by which the current may be led into two different circuits in turn.

Several improved forms of reverser are now made where the mercury poles are replaced by brass banks, and these are generally to be preferred in practice.

(2) INDUCED CURRENTS. In using these the muscle or nerve is stimulated by the current of momentary duration produced in the secondary circuit of an induction coil by the make or break of a constant current in the primary.

The construction of the induction coil or *inductorium* is founded on the fact that, if a coil of wire in connection with a galvanometer be placed close to (but insulated from) another coil through which a current may be led from a battery, it is found that on make and break of the current of the second coil a momentary current is induced in the

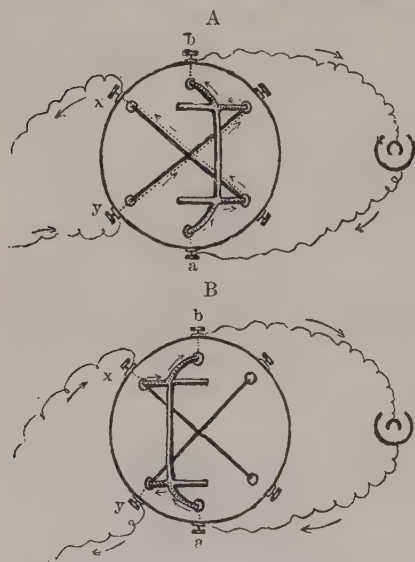


FIG. 44. Diagram of Pohl's Reverser.

first. The induced current on make is in the reverse direction, that on break in the same direction as the primary current. The electromotive force of the induced current is proportional to the number of turns of wire in the coils. The induction coil consists of two coils, each containing many turns of wire. The smaller coil (R_1 , Fig. 45), consisting of a few turns of comparatively thick wire, is the primary coil and is put into connection with a battery. It has within it a core of soft iron wires, which has the effect of concentrating the lines of force, and so increasing its power of inducing secondary currents. The secondary coil, R_2 , of a large number of turns of very thin wire, is arranged so as to slide over the primary coil. It is provided with two terminals, which may be connected with the nerve or other tissue that we wish to stimulate. Since the electromotive force of the induced current is proportional to the number of turns of wire, the electromotive force of the current delivered by the induction coil may be many thousand times that of the battery current flowing through the primary coil. The induced currents increase rapidly in strength as the coils are approached to one another; the strength of these therefore may be regulated by pushing the secondary up to or away from the primary coil.

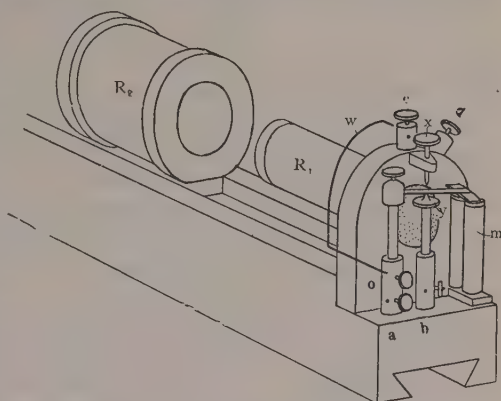


FIG. 45. Diagram of Inductorium. R_1 , primary; R_2 , secondary coil; m , electro-magnet of Wagner's hammer; w , Helmholtz's side wire.

A short-circuiting key is always placed between the secondary coil and the nerve to be stimulated. If only single induction shocks are to be used, a make-and-break key is put in the primary battery circuit, and the two wires from the battery and key are attached to the two top screws of the primary coil (c and d , Fig. 45).

It is found that the shock given by the induced current on break of the primary current is much stronger than that on make. In endeavouring to explain this difference in the intensity of the make-and-break induction shocks, it must be remembered that the intensity of the momentary current induced in the secondary coil at make or break of the primary current is proportional (1) to the number of

turns of wire in each coil; (2) inversely to the mean distance between the coils (*i.e.* the nearer the coils, the stronger the induced current); (3) to the rate of change in strength of the primary current. When a current is made through the primary coil, induction takes place, not only between primary and secondary coils, but also between the individual turns of the primary coil itself. This current of self-induction, being opposed in direction to the battery current, hinders and delays the attainment by the latter of its full strength, and so slows the rate of change of current in the primary coil. Hence the intensity of the momentary current

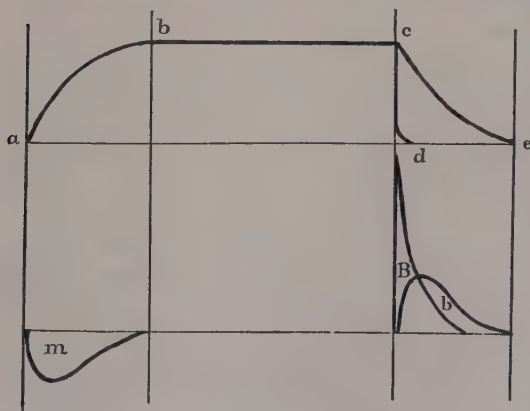


FIG. 46.

induced in the secondary coil is less than it would have been without the retarding effect of self-induction. At break of the current, an extra current is also produced in the primary coil in the same direction as the battery current, and therefore tending to reduce the rate of change of the current from full strength to nothing. In this case however the primary circuit being broken, the current of self-induction cannot pass without jumping the great resistance offered by the air, so that its retarding effect on the rate of disappearance of the primary current may be practically disregarded. In Fig. 46 the line,

a, b, c, d, will represent the changes occurring in the primary current at make and break, a b corresponding to the make and c d to the break. The lower line represents the momentary currents induced in the secondary circuit, m being the current of low intensity and long duration produced by the make, and n the shock of high intensity and short duration caused by the sharp break of the primary current.

When we desire to use faradic stimulation—that is, secondary induced shocks rapidly repeated 50 to 100 times a second—we make use of the apparatus attached to the coil, known as Wagner's hammer (Figs. 47A and 47B). In this case the wires from the battery are connected to the two lower screws (a and b, Fig. 47). Fig. 47A shows the direction of the current when Wagner's hammer is used. The current enters at a, runs up the pillar and along the spring to the screw x. Here it passes up through the screw and through the primary coil R_1 . From the primary coil it passes up the small coil m, and from this to the terminal b and back to the battery. But in this course the coil m is converted into an electro-magnet. The hammer h attached to the spring is attracted down, and so the spring is drawn away from the screw x, and the current is therefore broken. The break of the current destroys the magnetic power of the coil, the spring jumps up again and once more makes circuit with the screw x, only to be drawn down again directly this occurs. In this way the spring is kept vibrating, and the primary circuit is continually made and broken, with the production at each make-and-break of an induced current in the secondary coil.

When the primary current is made and broken fifty times in the second, there will be a hundred momentary currents produced during the same period in the secondary

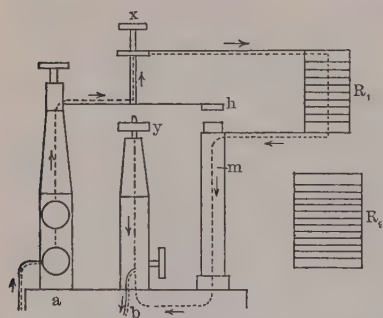


FIG. 47A. Diagram showing Course of Current in Inductorium when Wagner's Hammer is used.

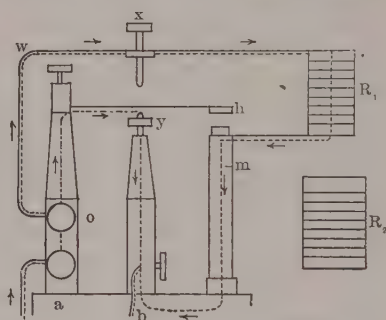


FIG. 47B. Diagram showing Course of Current when the Helmholtz Side Wire is used.

coil. Every alternate one of these produced by the break of current in the primary will be much stronger than the intervening currents produced by the make. In order to equalise make-and-break induction shocks, so that a regular series of momentary currents of nearly equal intensity may be produced, the arrangement known as Helmholtz's is used. In this arrangement the side wire w, shown in Fig. 45, and diagrammatically in Fig. 47B, is used to connect the binding screw o with the binding screw c at the top of the coil. The screw x is raised so as not to touch the spring, and the lower screw y is moved up till it comes nearly in contact with the under surface of the spring. If we consider the direction of the current now, we see that it enters as before at the terminal, travels up the Helmholtz wire w to the screw x, thence through the primary coil R_1 , and through the coil m of the Wagner's hammer back to the battery. The coil m, thus becoming an electro-magnet, draws down the hammer h. In this act the under-surface of the spring comes in contact with the screw y. The current then has a choice of two ways. It may either go through the coil as before, or take a short cut from the terminal a, up the pillar, along the spring, through the screw y, and down to the terminal b back to the battery. As the resistance of this latter route is very small compared with the resistance of the primary coil, &c., the greater part of the current takes this way. The infinitesimal current which now passes through the coil of Wagner's arrangement is insufficient to magnetise this, and the hammer springs up again; thus the process is restarted, and the spring vibrates rhythmically. With this arrangement the primary current is never broken but only short-circuited, and so diminished very largely. Hence the retarding influence of self-induction is as potent with break as with make of the current, and the effects on the secondary coil in the two cases are approximately equal. In Fig. 46 ce represents the change in the primary current when the current is short-circuited instead of being

broken, and *b* represents the effect produced in the secondary coil. It will be seen that the currents *m* and *b* are practically identical in intensity and duration.

When the induction coil is used for stimulating, it is usual to graduate the strength of the shock administered to the excitable tissue by moving the secondary coil nearer to or further away from the primary coil. It must be remembered that the strength of the induced current does not vary in numerical proportion with the distance of the two coils from one another. The increase will become more and more rapid as the two coils are brought closer together. Using the same strength of current in the primary coil and the same resistance in the secondary coil, we can say that the make-or-break current will be uniform so long as the distance of the coils remains constant. If it is required to know the exact increment in the exciting current which is used, it is necessary to graduate the induction coil by sending the induction shocks, obtained at different distances of secondary from primary coil, through a ballistic galvanometer.

Another method which may be adopted for the excitation of muscle or nerve is the discharge of a *condenser*. If two plates of metal separated from one another by a thin insulating layer of dielectric such as air, glass, mica or paraffined paper, be connected with the two poles of a battery, each plate acquires the potential of the pole of the battery with which it is connected, and receives therefrom a charge of electricity (positive or negative). If the connections be broken the two plates retain their charge. If now they be connected by a wire they discharge through the wire, and if a nerve be inserted in the course of the wire, it may be excited by the discharge.

The amount of electricity that may be stored up in this way will depend on the extent of the plates and their proximity to one another, as well as on the E.M.F. of the charging battery. In order to get great extent of surface, a condenser is built up, as in the diagram (Fig. 48), of a very large number of plates of tinfoil, separated by discs of mica or paraffined paper. Alternate discs are connected together: thus 1, 3, 5 are connected to one pole while 2, 4, 6 are connected to the other.

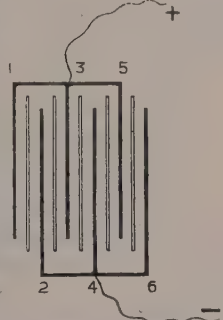


Fig. 48. Diagram to show the Mode of Construction of a Condenser.

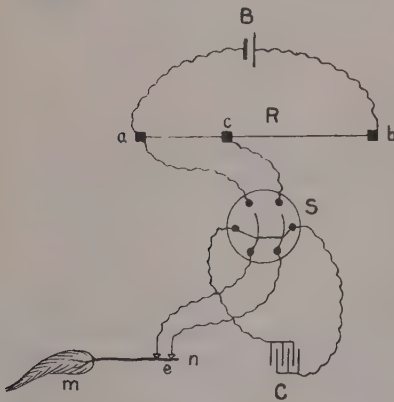


Fig. 49. Arrangement of Apparatus for the Excitation of a Nerve by means of Condenser Discharges.

B, battery; R, rheocord; c, rider of rheocord; s, switch (Pohl's reverser without cross wires); c, condenser; n, nerve; m, muscle; e, non-polarisable electrodes.

The condenser discharge is especially useful when we desire to determine the total amount of energy involved in the electrical stimulation of a nerve or muscle. The arrangement of such an experiment is shown in Fig. 49. By means of the switch *S* the condenser can be put into connection either with the battery from which it receives its charge or with the nerve through which it can discharge. By knowing the capacity of the condenser and the electromotive force by which it is charged, we can estimate the energy of the charge sent through the nerve.

$$E \text{ (energy in ergs)} = \frac{1}{2} CV^2$$

(*C* = capacity in microfarads; *V* = electromotive force in volts).

In this way it has been found that the energy of a minimal effective stimulus for frog's nerve is about $\frac{1}{1000000}$ of an erg.

The amount of energy necessary to excite the nerve will vary with the rate at which the condenser discharges through the nerve.

The *rheocord* or *potentiometer* is used to modify the amount or strength of current flowing

through a preparation. One form of it is represented in Fig. 50. A constant source of current at *B* causes a flow of electricity from *a* to *b* through a straight wire. As the resistance of this wire is the same throughout its length, the fall of potential from *a* to *b* must be constant. The nerve, or whatever preparation is used, is connected with the

straight wire at two points, at *a* and at *c*, by means of a sliding contact or rider. Supposing that there is an electromotive difference of one volt between *a* and *b*, if *c* is pushed close to *b*, the E.M.F. acting on the nerve will be also one volt. The E.M.F. however may be made as small as we like by sliding *c* nearer to *a*. Thus if *a b* is one metre and there is a difference of one volt between the two ends, then if *c* be one centimetre from *a*, the E.M.F. acting on the nerve will be $\frac{1}{100}$ volt. Thus we graduate the current passing through the nerve by altering the E.M.F. which drives the current.

If a weak *constant current* be passed through a muscle or any part of its nerve, at the make of the current the muscle gives a single sharp

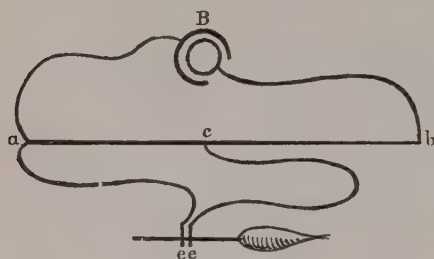


FIG 50.

contraction — a *muscle twitch*, in which the whole of the muscle fibres may be involved. During the passage of the current no effect is apparently produced and the muscle seems to be quiescent, though on careful observation we may see that there is a state of continued contraction limited to the immediate neighbourhood of the cathode, which lasts as long as the current is passing through the muscle, and is not propagated to the rest of the muscle.

If the current be now broken, the muscle may remain quiescent, but if the current is above a certain strength, the muscle responds to the break of the current with another single twitch. With a current of moderate strength we may get a contraction both at make and break of the current, the make stimulus being more effective than the break stimulus.

Besides this difference in intensity at make and break of the constant current, there is a difference in the point from which excitation starts. *A make contraction starts from the cathode, a break contraction from the anode.* This is well shown by the two following experiments.

(a) A curarised sartorius muscle of the frog (Fig. 51), with its bony insertions still attached, is fastened at the two ends to two electrodes, which are able to swing when the muscle contracts, and are attached by threads to levers which serve to record the contraction. The middle of the muscle is then fixed by clamping it lightly.



FIG. 51. Sartorius clamped in middle and attached to levers at either end.

The middle of the muscle is then fixed by clamping it lightly. A circuit is arranged so that a constant current can be sent through the electrodes and the whole length of the muscle. It is found, on making the current, that the lever attached to the cathode—that is to the electrode by which the current leaves the muscle—rises before the other lever. On the other hand, on breaking the current, the lever at the anode rises first, showing that the anodic half of the muscle contracts before the cathodic half.

(b) The irritability of a muscle, *i.e.* its power of responding to a stimulus by contracting, is dependent on the life of the muscle. If the muscle be injured or killed at any spot, its irritability at this spot will be therefore diminished or destroyed. Hence if we stimulate a muscle at the injured spot, no contraction will ensue. This fact may be used to demonstrate the facts of polar excitation. A muscle with

parallel fibres, such as the sartorius, is injured at one end, and a constant current passed, first from the injured to the uninjured end, and then in the reverse direction (Fig. 52). It is found in the former case, when the anode is on the injured part (which is therefore less excitable), that break of the current is ineffective, and in the latter, when the cathode is on the injured surface, that the make stimulus is ineffective, showing that the part excited corresponds to the cathode at make and to the anode at break.

With a current of very short duration no excitation is produced at break. Every induction shock is such a current of very short duration produced in the secondary coil by make or break of the primary circuit, and can be therefore regarded as a make stimulus, and when such a shock is led through a muscle the contraction in each case will start at the cathode, *i.e.* the point at which the induction shock leaves the muscle. The results of stimulating nerve fibres are similar to those obtained by stimulating muscle fibres directly.

Using the *induced current* as a stimulus, it is found that the contraction on break of the primary current is much stronger than that on make. It must not be imagined however that there is any contradiction between this and the fact that the make of a constant current is a stronger stimulus than the break. When we make a current in the primary, there is a current of momentary duration induced in the secondary, so that there is a rise and fall of current through the muscle; and the same thing takes place again when the primary circuit is broken. It has been shown that, when we use currents of such short duration, the fall is ineffective; so in both cases, whether we make or break the current in the primary circuit, we are dealing with a *make* stimulus in the muscle. The difference in the efficacy of make-and-break induction shocks is purely physical, and depends on the fact that the current induced in the secondary coil on make is of slower rise and smaller potential than that produced at break.

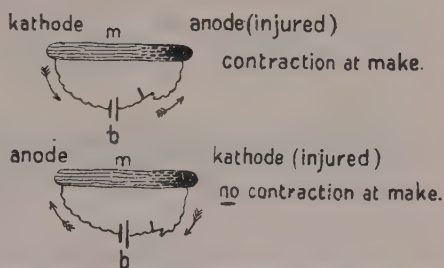


FIG. 52. Diagram to show the Effect of Local Injury on the Excitability of a Muscle. *b*, battery; *m*, muscle. The arrows indicate the direction of the current.

In using either of these modes of stimulation we find that there is a certain intensity which the stimulating current must possess in order that any effect shall be produced. Any strength of stimulus below this is known as a *subminimal* stimulus. A *minimal* stimulus (sometimes known as *liminal* or *threshold* stimulus) is the weakest stimulus that will produce any result, *i.e.* in muscle a contraction. With galvanic excitation, this is also called the *rheobasic strength*. A *maximal* stimulus is one that produces the strongest contraction a muscle is capable of under the effects of a single stimulus. A *submaximal* stimulus is any strength of stimulus between these two extremes.

As will be seen later, the *duration* of the flow of current also affects the result when short periods of flow are concerned.

EXCITABILITY AND CHRONAXIE

Examination of the properties of different living tissues demonstrates that their excitabilities vary widely. Some tissues require on galvanic stimulation a much stronger current than others, or, on faradic stimulation,

a closer coupling of the secondary to the primary coil. Again, some respond to galvanic but not to faradic excitation, or *vice versa*. It is clear that comparison of excitabilities in different tissues is unsatisfactory, if at all possible, on such indications as these. In view of the fact that there is no fundamental qualitative difference between galvanic and faradic currents, such a statement as "excitable to faradic, inexcitable to galvanic electricity," so often met with, is meaningless.

Dealing with galvanic stimulation as more readily analysable than faradic, it is found that the following must be taken into account in studying excitability :—

(a) *The current density* or strength of current (c) or else the *voltage* (V)—to which (c) is proportional—required to stimulate.

(b) *The duration of flow* of the current. It has been found that a current that will just excite when of a particular duration, fails to do so when its duration is reduced below a certain level ; also, for a given current beyond

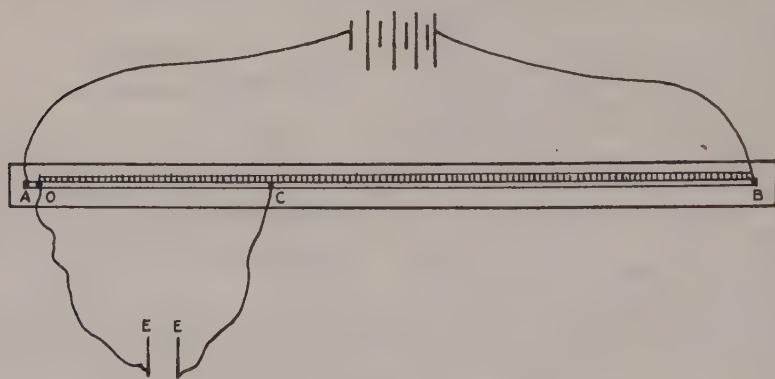


FIG. 53. Simple Liquid Potentiometer.

a particular duration, differing for each tissue, further continuation of the current produces no further effect.

An elementary illustration, given by Lapicque, will serve to show the importance of the time factor in excitation. A liquid potentiometer is used consisting of a long narrow trough filled with zinc sulphate solution. Into it dip two plates of amalgamated zinc A and B (Fig. 53), placed about one metre apart and connected with the source of current ; two other similar plates also dip into the gutter ; O is stationary and near to A, while C can be dipped in and out of the solution, thus making and breaking contact. The electrodes EE are placed in contact with a strip of plain muscle (frog's stomach). The strength of current flowing through the tissue is proportional to the distance of C from O. If C be plunged into the groove at intervals of a few seconds, further and further from O at each immersion, a point, the *threshold* will be reached, at which each prolonged immersion is followed by contraction of the plain muscle. The distance OC at which this occurs (say 10 cm.) is noted. Now C is withdrawn and dipped as quickly as possible in and out of the groove at the same point, giving stimuli lasting only about one-tenth of a second ; no contraction will result. If the distance OC is made greater, however (say 70 cm.), so as to increase the potential tapped off, even this brief duration will stimulate.

(c) *The rate of change* of the current strength. In (a) and (b) it has been assumed that the current was established and stopped instantaneously

("rectilinear waves") as in Fig 54 (A), whereas under certain circumstances a current might fluctuate by a slope, *e.g.* as shown in Fig. 54 (B), and these fluctuations would need to be taken into account. If, instead of plain muscle, the nerve of a frog's sciatic-gastrocnemius preparation be placed on the electrodes EE, and the cursor C of Fig. 53 be *quickly* moved along the groove, say, from O to 20 cm., so as to cause a rapidly increasing current to flow through the nerve, the latter will be stimulated as shown by contraction of the muscle. Now return the cursor to O and move it away *very slowly*; it will be found that although it be moved far beyond the previous distance (say to 50 cm.), no contraction will follow—the slow slope of current-increase is ineffective, whereas the steep gradient stimulated the nerve.

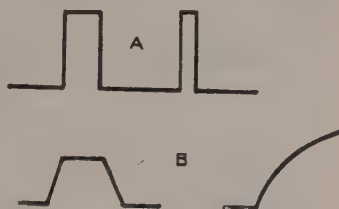


FIG. 54.

Du Bois Reymond expressed this fact by stating that excitation depends on the rate of variation of current density from moment to moment; the more rapid the change the greater the excitatory effect.

This statement is now known to be only partially true. We should now regard it as more correct to say that the current excites during the first moment of its passage, whether variable or constant, but that a certain duration of flow is essential.

To demonstrate the importance of duration in the stimulation of such highly excitable tissues as nerve or striated muscle we require much more refined apparatus than that described above for use with the relatively inexcitable plain muscle. If we can get currents of sufficiently short duration, we can demonstrate that with *any* tissue a minimal current which will excite at a longer duration fails to do so when it is abbreviated beyond a certain limiting value. This limit for the frog's stomach is of the order of tenths of a second, while for the sciatic nerve it is of the order of thousandths of a second.

These simple considerations serve to illustrate the importance of the time factor in excitation, and to show that "slow" and "rapid" are purely relative terms when different tissues are under consideration.

Currents of sufficiently short duration can be obtained by the use of a mechanical device or rheotome, such as Lucas's pendulum or spring (Fig. 55), by which two keys are opened at known intervals. The first key is a short circuiting

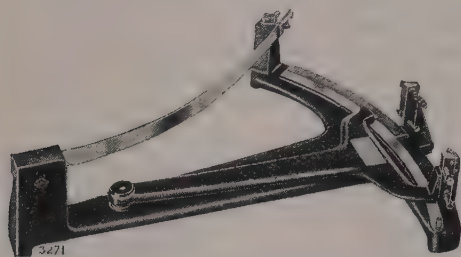


FIG. 55. Keith Lucas's Spring Rheotome.

key, the opening of which starts the current, and the second one is in series, and its opening stops the current.

Another method is by the use of condenser discharges. The time taken for a condenser to discharge can be calculated if its capacity and the resistance of the circuit are known, the time being proportional to the product RC . The current strength is, of course, not constant during the discharge, but it is much easier to obtain currents of very short duration by the adjustment of condenser capacities than by any of the rheotomes for use with constant currents, and the drawbacks attendant on the use of discharges of rapidly declining strength have been overcome, since it has been shown that a

discharge from a condenser charged to a given voltage is equivalent to a rectilinear constant current of duration $= 0.37 RC$ seconds, at the same voltage (R = resistance of circuit in ohms ; C = capacity of condenser in farads).

When the smallest voltages which will excite a tissue are plotted against the durations of the current, controlled in either of these ways, a curve of the rectangular hyper-

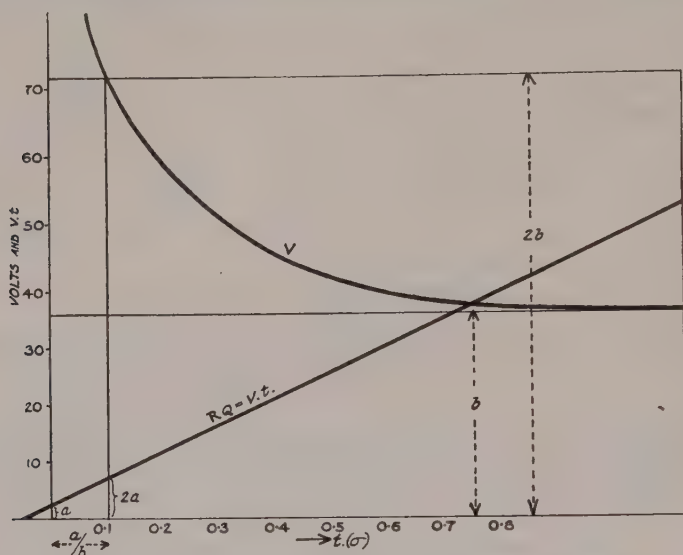


FIG. 56. To illustrate Weiss's Laws and their Relation to Chronaxie. V = curve of voltages. RQ = curve of quantities. $a = 3.5$.

$b = 36$ volts. $\frac{a}{b} = c \cdot 0.1\sigma$ = chronaxie. Abscissæ = time in 0.1σ .

Ordinates figured = volts. Ordinates for $RQ = Vt$ are on same scale. (Modified from BOURGUIGNON. *La Chronaxie*.)

bola type (Fig. 56) is obtained, one of the asymptotes of which is a line at the level of the threshold voltage (b) for currents of infinite duration.

If the quantities of electricity (proportional to Vt) are plotted against times, a straight line is obtained.

These relations are expressed for constant currents by Weiss's laws :—

(1) For intensity,

$$i = \frac{V}{R} = \frac{a}{t} + b.$$

(2) For quantity,

$$Q = it = a + bt,$$

where a and b are two constants.

a is the quantity of electricity where the graph cuts the ordinate.

b is the threshold strength at infinitely long duration. Almost identical relations are obtained by the use of condensers (Hoorweg's laws).

Lapicque calls the liminal value for indefinite duration (galvanic threshold) the *rheobase*, and estimates the excitability of a tissue by what he has called the *chronaxie*.

The *chronaxie* may be defined as the shortest duration of twice the rheobasic strength which will stimulate. Thus in Fig. 56, when the voltage is raised to $2b$, the shortest duration which will excite is 0.1σ ,* and this duration is the *chronaxie*. A less excitable tissue has a longer, and a more excitable one a shorter *chronaxie*.

* 1σ (sigma) = $\frac{1}{1000}$ second.

In practice, in order to determine the chronaxie, all that is necessary is to find the galvanic threshold or rheobase, using an ordinary key, double the voltage so employed, and then, using either condensers or a suitable rheotome, find the shortest duration of this which will excite.

The chronaxie of a tissue is a definite measure of its excitability, since in this time a current of twice the rheobasic strength is able to produce those physico-chemical alterations which determine excitation, and the more excitable the tissue is, the more quickly will that current produce those changes. It can be shown that what happens in an excitable tissue in, say 3/10,000 of a second, may require, say, eight seconds for a very inexcitable one.

The following table shows some approximate chronaxies for excitable tissues of very varying types:—

Tissue.	Chronaxie (σ).	Approximate Duration of Contraction of Muscles.
		Seconds.
Frog's gastrocnemius (esculenta).	0.3 σ	0.1
" " (temporaria)	0.7 σ	0.1
Toad's sciatic gastrocnemius	1.3 σ	0.16
Frog's ventricle	3.5 σ	1.0-2.0
Tortoise heart (testudo græca)	8.2 σ	2-3
Claw muscle of crab	30 σ	5
Frog stomach	30-100 σ	15-20
Pigment cells, skin of frog	1,000-15,000 σ	—

It is evident from consideration of the figures for different chronaxies that there is a relation between chronaxie and speed of action of tissue. The more excitable tissue has, as a rule, a shorter chronaxie, shorter period of action, shorter refractory period, and a quicker rate of propagation, than a less excitable one.

It is because of its very short duration (0.1 σ) that the induced current is unable to effect the excitation of sluggish tissues such as some forms of plain muscle. When the duration is made extremely short, even high voltages fail to excite the most irritable tissues. Hence high frequency (Tesla) alternating currents of enormous voltage can be passed through the body without any physiological effect.

Summation of Stimuli. Closely associated with the chronaxie of the tissues are the phenomena of 'summation of stimuli' and of 'refractory period.' If two subminimal stimuli are sent in within a sufficiently short interval of time, their effect is summated so that two stimuli, each of which would be ineffective, may together produce an excitation. For summation of two stimuli to take place, the second stimulus must occur at a time before the condition excited by the first stimulus has died away. The maximum time at which summation can take place will therefore vary from tissue to tissue, and will bear a relation to the chronaxie. This is evident if we compare the maximum summation intervals for different tissues with their chronaxies. Thus for frog's nerve, with a chronaxie of 0.3 σ , the summation interval is 0.5 σ , while for frog's heart, with a chronaxie of about 3.5 σ , the maximal summation interval is 8.0 σ .

The Law of Isochronism. The same chronaxie is found for a muscle stimulated directly or *via* its nerve. The classical view was that the muscle is much less excitable than its motor nerve, and that between the nerve and the muscle there is interposed a material, related to the motor end plate

and having special properties, by which the excitation is passed from nerve to muscle. Much of the argument for the existence of this material has turned on the action of drugs, *e.g.* curari, which was believed specifically to poison this "receptor substance." Lapicque's explanation is entirely different. He believes approximate *isochronism* of nerve and muscle is a necessary condition for the transmission of the excitatory condition from nerve to muscle, and failure of transmission may be expected to happen when the chronaxie of the muscle differs from that of its nerve by about 100 per cent.

Examination of the action of those drugs which abolish the transmission supports this hypothesis. Curari and sparteine act by increasing the chronaxie of the muscle, that of the nerve remaining unaltered. Strychnine (0.25 per cent.) on the other hand reduces the chronaxie of nerve without changing that of muscle.

In any case as soon as the chronaxie of either tissue is double that of the other, conduction fails; by the further action of the drug much greater discrepancies in chronaxie are reached.

PROPAGATION OF CONTRACTION

The whole muscle does not as a rule contract simultaneously. When excited from its nerve the contraction begins at the end plates and spreads in both directions through the muscle. The rate of propagation of the contraction wave can be measured only by employing a curarised muscle, so as to avoid the wide spreading of the excitatory change by means of the intra-muscular nerve endings. For this purpose a curarised sartorius muscle is stimulated at one end, and the thickening of the muscle recorded by means of two levers placed one near the exciting electrodes and the second at the other end of the muscle, as shown in the diagram (Fig. 57). The

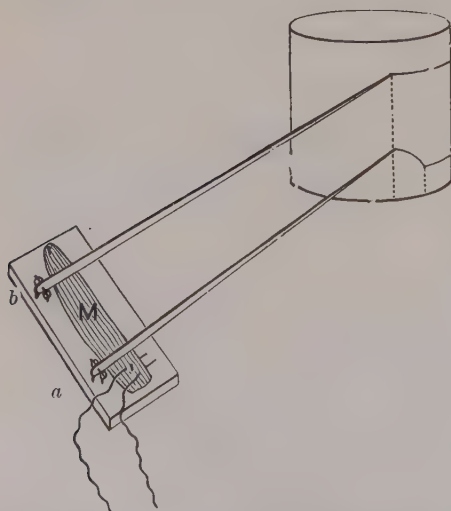


FIG. 57. Diagram of Arrangement for recording the Contraction Wave in a curarised Sartorius.

difference between the latent periods of the two curves represents the time taken by the contraction wave in travelling from *a* to *b*. By measurements carried out in this way it is found that the rate of propagation of the contraction in frog's muscle is 3 to 4 metres per second; in the muscle of warm-blooded animals it may amount to 6 to 12 metres. Similar, but more accurate results are obtained by following the passage of the electrical variation along the muscle.

The actual duration of the shortening at any given point amounts in frog's muscle to only 0.05–0.09 sec. The length of the wave is obtained by multiplying the rate of transmission by the duration of the wave at

any one point. It varies therefore in frog's muscle between 3000×0.05 ($= 150$) and 4000×0.09 ($= 360$) millimetres. Thus the muscle fibres in the frog are much too short to accommodate the whole length of the wave, and the contraction of the whole muscle must be made up of the summated effects of the contraction wave as it passes from point to point. Hence

the longer the muscle, the more must the contraction be lengthened by the time taken up in propagation from one end to another.

THE MECHANICAL CHANGES THAT A MUSCLE UNDERGOES WHEN IT CONTRACTS

If a skeletal muscle, such as the gastrocnemius, be stimulated either directly or by the intermediation of its nerve, it responds by a single short, sharp contraction, followed immediately by a relaxation. The volume of

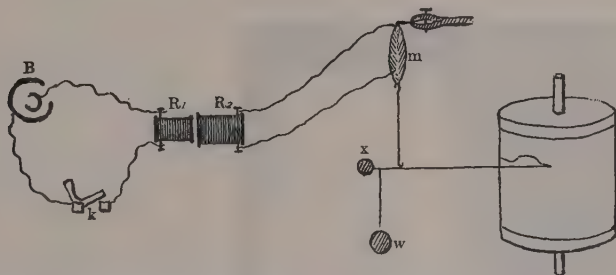


FIG. 58. Arrangement of Apparatus for recording simple Muscle Twitch.

the muscle does not alter, but each muscle fibre and the whole muscle become shorter and thicker. At the same time, if a weight be tied on to the tendon of the muscle, the muscle during contraction may raise the weight and thus perform mechanical work. To determine the time relations of the simple muscle contraction or twitch, and to study its conditions, it is necessary to employ the graphic method.

In order to record the contraction of the frog's gastrocnemius, the muscle is excised together with a portion of the femur to which it is attached, and often with the whole length of the sciatic nerve. The femur is clamped firmly, and the tendo Achillis attached

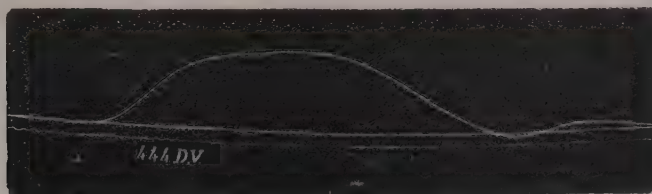


FIG. 59. Curve of single Muscle Twitch taken on a rapidly moving surface. (Yeo.)

by a thread to a light lever, free to move round an axis at one end. The point of this lever is armed with a writing point, which just touches the blackened surface of a piece of glazed paper stretched round a cylinder (drum) which can be made to rotate at a constant speed. If the drum is moving, the point draws a horizontal white line on the smoked paper.

If a single induction shock be sent through the nerve of the preparation, the lever is jerked up, falling again almost directly, and a curve is drawn like that shown in Fig. 59. A similar curve is obtained if the muscle be stimulated directly (Fig. 58).

In all such graphic records we should have also—

(1) *A time record.* This is furnished by means of a small electro-magnet, armed with a pointed lever writing on the smoked surface. This electro-magnet (time marker or signal) is made to vibrate 100 times a second (more or less as may be required) by putting it in a circuit which is made and broken 100 times a second by means of a tuning fork vibrating at that rate. The tuning fork is maintained in vibration in the same way as the Wagner's hammer of an induction coil,

(2) A record of the exact point at which the nerve or muscle is stimulated. This may be obtained in two ways :

(a) A trigger key is so arranged that a projecting arm of the drum strikes it, and breaks the primary current of an induction coil, as the drum revolves. To mark the moment of excitation as the graphic record, the drum is moved slowly by hand, till it just breaks the circuit and excites the muscle. As the drum is not moving, the muscle writes in this way its own moment of excitation.

(b) If we wish to make and break the primary circuit at will by means of a key, a small electro-magnetic signal, interposed in the circuit, is arranged to write on the revolving drum, and so mark the point of stimulation.

In Fig. 59 the upper line is the curve drawn by the lever of the muscle as it contracts ; the small upright line shows the point at which the muscle was stimulated ;

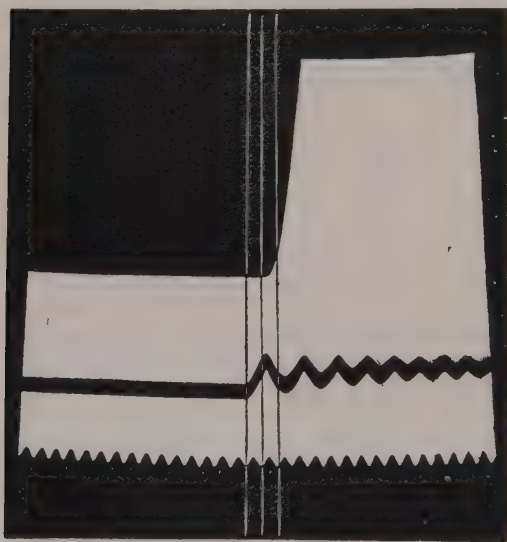


FIG. 60. Photographic Record of Muscle Twitch. (BURDON-SANDERSON.) The upper curve is the movement of the muscle, the middle curve the signal showing the moment of excitation, and the lower curve is that of a tuning-fork vibrating 500 times a second.

In the first case the energy of the moving mass will be proportional to $40 \times (1)^2 = 20$, and in the second to $\frac{1 \times (40)^2}{2} = 800$, and it is this energy which determines the overshooting of the lever and the deformation of the curve. In the method just described, the lever follows the muscle in its movement, the tension on the muscle remains the same throughout, and the method is therefore known as the *isotonic method*.

A simple *isotonic contraction* or twitch, such as that in Fig. 59, produced by a single stimulus, consists of three main phases :

- (1) A phase during which no apparent change takes place in the muscle. This is called the *latent period* (Fig. 60).
- (2) A phase of shortening or *contraction*.
- (3) A phase of *relaxation* or return to the original length.

The small curves seen after the main curve are due to elastic vibrations of the lever. The latent period occupies about $\frac{1}{100}$ second, the phase of shortening $\frac{4}{100}$ and the relaxation $\frac{5}{100}$ second.

Thus a single muscle twitch in a frog is completed in about $\frac{1}{10}$ second. It must be remembered however that this figure is only approximate, and varies with the temperature of the muscle and its condition, being much longer in a fatigued muscle. It depends also on the animal from which the muscle is taken. In the tortoise a

and the second line is the tracing of the chronograph, every vibration representing $\frac{1}{114}$ of a second.

The graphic record may, in consequence of instrumental inertia, be a very inaccurate reproduction of the true events occurring in the muscle itself. When the muscle begins to contract, it imparts a very rapid movement to the lever which therefore tends to overshoot the mark and deform the curve. This source of error may be almost avoided by making the lever as light as possible, and hanging the extending weight in close proximity to the axle of the lever, as shown in Fig. 58. Since the energy of a moving mass is proportional to the square of the velocity ($= \frac{1}{2}mv^2$) and the tension due to the weight as well as the velocity imparted to the weight on contraction is directly proportional to the distance of the weight from the axis, it follows that it is better to load the muscle with 40 grammes 1 millimetre from the axis than with 1 gramme 40 millimetres from the axis, though the tension put on the muscle will be the same in both cases.

single twitch may last from half a second to five seconds, according to temperature. In the wing muscle of a wasp the duration of a single contraction may be only $\frac{1}{300}$ sec. It is almost impossible to avoid some deformation of the curve due to defects of the recording instruments used. Thus the period during which no mechanical changes are taking place in the muscle must always be shorter than is apparent from a curve obtained by the foregoing method. The elasticity and extensibility of the muscle must prolong the apparent latent period, since the first effect of contraction of any part of the muscle will be to stretch the adjacent part, and only later to move the tendon to which the lever is attached. If we have a weight suspended by a piece of elastic, it will not follow a pull exactly but will lag behind, the first part of the pull being occupied with stretching the indiarubber, and only when this is stretched to a certain degree will the weight begin to rise. The same retardation of the pull would be observed if, instead of indiarubber, we used a piece of living muscle.

It is possible to obviate this instrumental inertia by employing photographic methods for the record. Such experiments were carried out long ago by Burdon-Sanderson, and show that the latent period is extremely short. The best criterion is the measurement of the interval between the commencement of the electrical response and the mechanical response. This period of 'true latency' is about 1.5 to 2.0σ ($1 \sigma = 0.001$ second) for frog and about 0.5σ for mammal (Liddell and Fulton). This is followed by a period called the period of *rigidity*, during which the muscle shortens very little, but enters into a rigid state. This lasts for 4 or 5σ in the frog and $2-3 \sigma$ in the mammal. The whole latent period is thus about 6σ for frog and 3σ for mammal. We shall have occasion later on to consider the changes which occur in the muscle during this period.

The relaxation of muscle is helped by a moderate load, and in a normal condition is complete. It is not active—that is to say, is not due to a contraction in the transverse direction—but is a passive effect of extension. This may be shown by allowing a muscle to contract while floating on mercury. The subsequent lengthening on relaxation is very incomplete.

It is of importance to be able also to record the development of the energy (*i.e.* the tension) of the active muscle apart from any changes in its length. For this purpose the muscle is allowed to contract against a strong spring, the movements of which are magnified. Thus the shortening of the muscle is almost entirely prevented, but the increase in its tension causes a minute but proportionate movement of the spring, which is recorded by means of the lever. Since in this case the length of the muscle remains approximately constant, while the tension is continually varying throughout the contraction, it is known as the *isometric method*. The great magnification necessary in this method necessitates the use of instruments having low inertias and very high natural vibration frequencies (about $1000-2000$ per second), as otherwise the record is deformed by the vibrations of the spring. The best arrangements are on the torsion-wire principle used by Sherrington, one type of which is shown in Fig. 61.

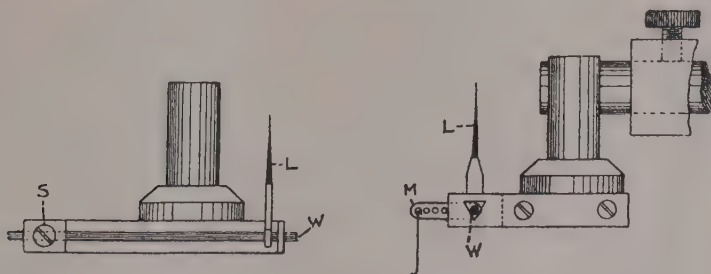


FIG. 61. Torsion-wire myograph for accurate records of tension changes in isometric contraction, showing the side and end views. W is a steel wire, fixed at S, and turning in the triangular slot, when twisted by the contractile force applied at M, to which the muscle is attached. L is a light steel needle, ground down at its terminal 2 mm. to a wire 0.06 mm. in diameter. The image of this thin extremity is projected through a microscope, and its movements recorded on a travelling photographic plate. (FULTON, from *Q.J. Exp. Phys.*)

The *isometric twitch* has a form roughly similar to the isotonic contraction, but differing from it in detail. The rise of tension commences very abruptly, is convex to the abscissa, and ends in a flattened plateau. Relaxation also commences suddenly, and gives a curve which is concave; the point at which contraction gives way to relaxation is definitely indicated by an "angle," and the duration of the contraction process is

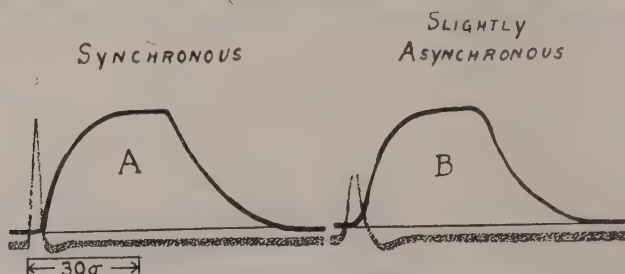


FIG. 62. Diagram showing the form of the isometric contraction curve and electric response when the fibres contract synchronously (A) and slightly asynchronously (B). (FULTON.)

given by the time intervening between the electrical response and the "angle." These features are only seen when the fibres all contract synchronously, as *e.g.* in an intact fresh muscle, with its circulation, stimulated indirectly (Fig. 62 A), and represent the course of events in individual fibres.

When isometric contractions are performed in the body, the curve is much smoothed out by reason of the fibres not all being synchronous. (Fig. 62 B).

Very considerable tensions are produced in isometric contractions, several hundred grams with a small frog's gastrocnemius. The duration of the contraction process is definitely *longer* in an isometric twitch than when the muscle is allowed to shorten (isotonic contraction); the duration is also increased by increasing the "initial" tension on the muscle, *i.e.* the stretch given to the muscle before its stimulation.



FIG. 63.

THE EFFECT OF STRENGTH OF STIMULUS.

THE 'ALL OR NONE' RULE. If a series of single break induction shocks be applied to a muscle at intervals of not less than five seconds, it will be found that beyond a certain distance of the secondary from the primary coil no effect at all is produced. The shocks are said to be sub-minimal. On pushing the secondary coil nearer the primary a point will be reached at which a small contraction will be observed. On then pushing in the coil a millimetre at a time the contraction will become greater for the next few centimetres (*e.g.* as the coil is moved from 12 to 10 cms. distance). Further increase of current by approximation of the coils is without effect, although the current actually used may be increased a hundred times in moving the coil from 10 to 0. It might seem that this limited gradation of the muscular response according to strength of stimulus was due to a similar gradation in the response of each individual muscle fibre of which the muscle is composed. The fact is, however, that when a minimal or submaximal response is obtained not all the fibres making up the muscle are contracting. A minimal

contraction is in fact a contraction in which *some* fibres of the whole muscle are stimulated. A maximal contraction is one in which *all* the fibres are stimulated. So far as concerns each individual muscle fibre every contraction is a maximal contraction. The rule of 'all or none' which was first enunciated for heart muscle is probably true for every contractile element. The

difference between skeletal and heart muscle lies in the fact that in the former the excitatory process does not spread from one fibre to its neighbours. If, for instance, we take a curarised sartorius and split its lower end as in Fig. 63, the stimulus applied to A causes a contraction only of the left side of the muscle, while a stimulus applied to B is in the same way limited to the right side. If a piece of ventricular or auricular muscle of the frog or tortoise were treated in the same way, a stimulus applied at A would cause a contraction which would travel across the bridge at the upper end and extend to B.

The 'all or none' law does not mean that it is impossible to vary *by any means* the extent of the mechanical response of a contractile tissue to stimulation, but only that such variations cannot be brought about by altering the strength of the stimulus.

The 'all or none' character of muscular contraction was indicated by Gotch and Keith Lucas, but the clearest demonstration of it is that given by the experiments of Pratt and Eisenberger. These investigators were able, by the use of micro-electrodes, to apply stimuli to individual fibres, while observing these directly under the microscope,

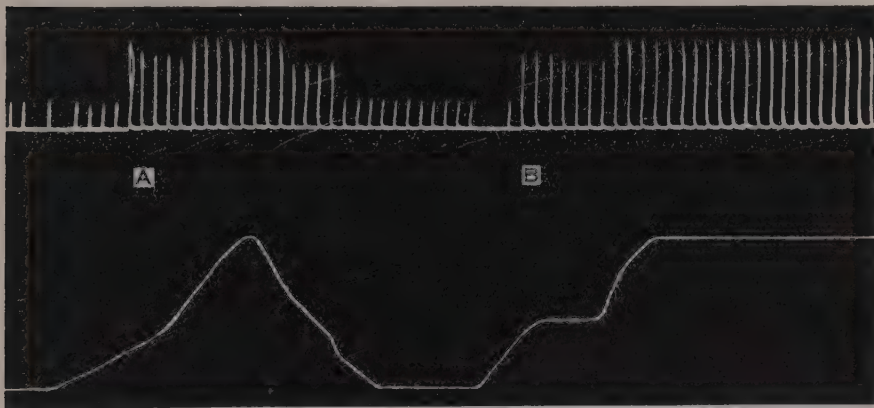


FIG. 64. Record of Contraction of Sartorius of Frog stimulated by break shocks from a 'pore' electrode. The record was made by photographing the excursion of a droplet of mercury on the surface of the muscle. Upper lining = extent of successive contractions; lower lining = variation in intensity of stimulus. (After PRATT and EISENBERGER.)

and also taking photomicrographic records of the extent of the contractions which resulted. One of these records is shown in Fig. 64. It will be noticed that, as the strength of the stimulus is steadily increased, the response increases in a series of steps, each of which was seen to correspond to the occurrence of contraction in a fresh fibre or fibres which had been unaffected by the weaker stimuli: each fibre which enters into contraction does so with maximal strength. The fine grading of muscular power is thus achieved by variation in the number of fibres brought into play.

THE REPETITION OF STIMULUS

SUMMATION OF CONTRACTIONS AND TETANUS. The response of a muscle fibre to a single shock, whether measured by the isotonic or the isometric method, *i.e.* as shortening or as tension, is independent of the strength of the stimulus and varies only with the length of the fibre during the rise of the excitatory condition. If however a second shock is sent in during this period a further evolution of energy is possible, and the effect is still further increased by putting a series of stimuli into the muscle or its attached nerve before the development of the contractile stress due to the first stimulus has reached its maximum. If two shocks at intervals of one hundredth of a

second be sent into a muscle, the response, whether shortening or rise of tension, will be greater than that produced by one shock (Fig. 65). The effects of the two stimuli are summated. (This phenomenon of summation of contractions must be clearly distinguished from that of summation of stimuli referred to previously.) If a series of shocks be sent in, the excitatory condition is maintained, so that instead of a simple muscle twitch rising to a

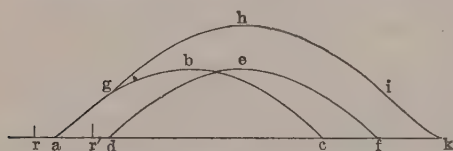


FIG. 65. Muscle Curves showing Summation of Contractions.

r and r' , the points at which the stimuli were sent into the nerve. From the first stimulus alone the curve abc would be obtained. From r' the curve def is obtained. These two curves are summated to form the curve $aghik$ when both stimuli are sent in at the interval $r r'$.

contraction produced by a series of stimuli may with a heavy load be three or four times as considerable as that produced by a single stimulus.

This type of summation may be called *wave-summation*, because it is due to the fusion of successive waves of contraction in the same fibres. This summation is not algebraical, *i.e.* the second contraction does not double the shortening brought about by the first, nor does it double the duration; the effect of the second stimulus is greater the earlier it falls during the first response.

Another type of summation is that called "*multifibre*" or *quantal* summation, which is due to an increase in the number of fibres responding, each fibre giving an all-or-none contraction. Thus in submaximal responses, as the strength of stimulation is increased, more and more fibres respond (synchronously). Or, again, when a mixed muscle containing fibres of different contraction durations (*e.g.* red and white fibres) is stimulated a summated contraction combining the features of both will result. Quantal summation is algebraical in character.

REFRACTORY PERIOD. If the interval between two stimuli sent into a muscle be successively shortened in a series of observations, we finally arrive at a point at which summation of contractions or of stimuli is no longer apparent, *i.e.* the effect of the two stimuli is no greater than the effect of a single stimulus. This means that the second stimulus has become ineffective, *i.e.* for a very short period of time after stimulation a muscle is inexcitable to a second stimulus. The period during which it is inexcitable is known as the refractory period and amounts in skeletal muscle to about 0.005 second. The same phenomenon is a common property of excitable tissues generally.

maximum and then falling, the muscle lever rises to a given point, which in the muscle contracting isometrically may be double or more that due to a single stimulus (Fig. 66), and then remains at this height during the continuance of the repeated excitations. The state of apparently continuous contraction evoked in a muscle by repeated shocks is called a *tetanus*. If the muscle be allowed to contract isotonicly, the continued

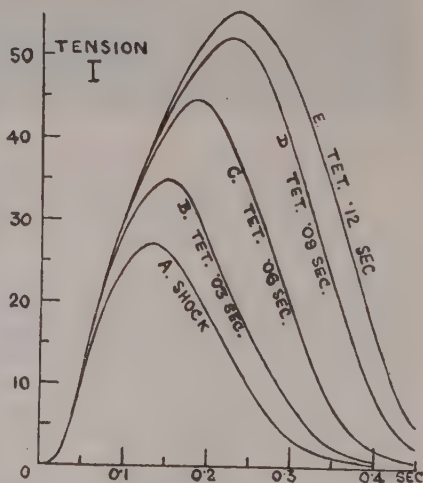


FIG. 66. Isometric Contraction Curves, showing continued rise of tension with prolongation of the excitation.

VOLUNTARY CONTRACTION

Under normal circumstances the contraction of skeletal muscles is brought about either reflexly, or in response to some stimulus descending from the cerebral cortex, the so-called 'voluntary contraction.' These contractions may have a duration of almost any extent. The quickest movements carried out by man have a duration of about 0.1 sec., but nearly all contractions last considerably over 0.1 sec. Since we have no certain means of producing contractions of any given length except by means of summation, it is natural that physiologists have regarded voluntary contractions as similar to the artificial tetanus produced by a summation of effect, either as wave summation or as quantal summation. In the belief that the response of each muscle fibre is invariably all or none in character, it must be admitted that the delicate gradation shown in the power of voluntary contractions is due to the participation of a variable number of fibres, the maximal force being exerted if and when all the fibres contract. Smoothness of contraction could be ensured by either mode of summation. Thus by a wave summation the same set of fibres would remain in a state of tetanic contraction through-

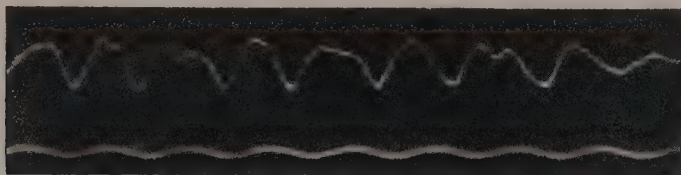


FIG. 67. Electrical Variations produced by Voluntary Contractions of Human Muscle. (PIPER.)

out, whereas in quantal summation different sets of fibres would work "in shifts," each fibre giving a short tetanus or even a single twitch.

It has often been supposed that definite information as to the nature of voluntary contraction would be obtainable by a study of the electrical variations or of the mechanical records, in the belief that the response was synchronous in all fibres; but the accumulated evidence of quantal summation of asynchronous contractions renders such investigations of doubtful value. An accurate method of recording the irregularities or oscillations in a contracting muscle—viz. the hot-wire method devised by A. V. Hill—has shown that they may attain to a frequency of more than 50 per second.

Piper led off two points in the forearm to a string galvanometer, one electrode being placed about two inches below the bend of the elbow and the other about four inches above the wrist. A single stimulus of the median nerve was found by him to give a typical diphasic variation in the muscles. When the muscles were contracted voluntarily, well-marked oscillations of the galvanometer wire were obtained, indicating the existence in the muscle of forty-eight to fifty complete diphasic variations in the second (Fig. 67). Piper obtained similar records on leading off other muscles of the body when these were placed voluntarily in a state of contraction, and he concluded therefore that each voluntary contraction, short or long, is a tetanus composed of about fifty fused twitches per second. These results are in agreement with the fact that the impulse, which normally travels down the motor nerve from the anterior cornual cell to the muscle, is discontinuous. Gasser and Newcomer have investigated the electrical changes accompanying the ordinary contractions of the diaphragm, and also those occurring in the phrenic nerve. They find both in the muscle and in the nerve that each contraction is accompanied by the discharge along the nerve of about seventy excitations per second. Adrian has shown that interrupted stimuli of up to 230 per second can be transmitted through the spinal cord and give rise to an identical rhythm in the muscles responding reflexly to the stimulation. This evidence is apparently in favour of the view that voluntary contraction and, one must add, the tonic contractions of all skeletal muscles are discontinuous in nature and analogous to the tetanus which we may evoke artificially by rapid stimulation either of muscle or of its motor nerve.

But it would be unsafe to infer from the rhythm of the electrical variations that the voluntary contraction is a tetanus resulting from the synchronous contraction at that rate of all the working fibres, since, as Fulton remarks, "we have no proof, from one action current deflection to the next, that the same group of fibres is in activity." Even in the case of simple reflexes such as the knee jerk, it can be shown for instance that a tetanus of several volleys gives rise to a single electrical response. When the higher centres are involved, as in voluntary contraction, the asynchronism of contraction is still more marked, and it is probable that when a rhythm is exhibited, each of the waves is the result of a short volley of excitatory impulses. Voluntary contraction thus appears

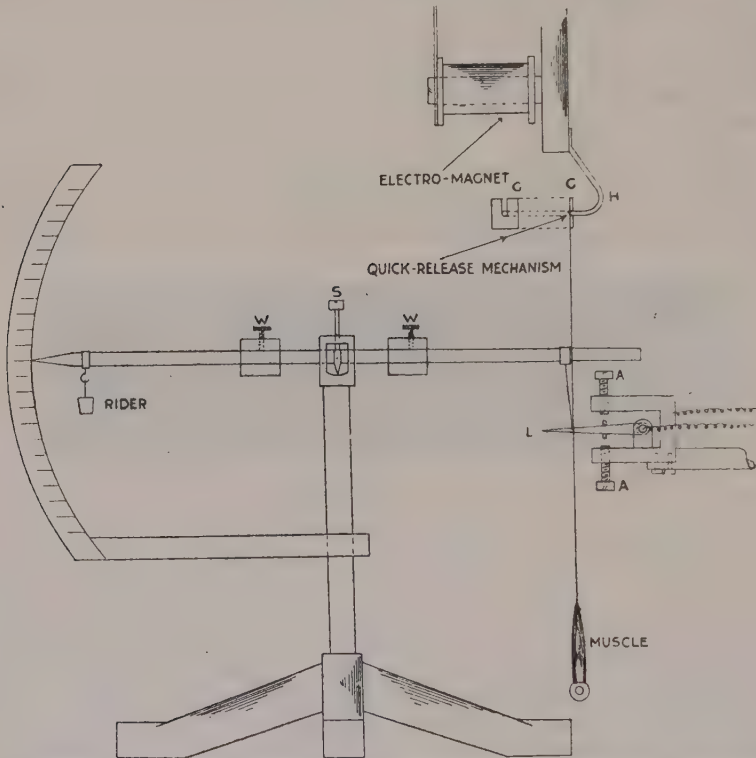


Fig. 68. Inertia Lever, with Weights W, W, and Screw S for adjustment of the centre of gravity on to the line of the knife edges. Rider and scale for measuring work. Lever L with adjustable stops A, A, for (1) limiting the extent of contraction, and (2) electrical timing of the duration of shortening. At the top, quick-release mechanism, withdrawing the stiff-wire H from between the guards G, and so releasing a loop on the fine wire holding the muscle stretched. (GASSER and HILL.)

to be a resultant of both forms of summation, or, in other words, to be a group of short tetani spread out in time to give an even contraction.

THE MECHANICAL ENERGY OF CONTRACTION

Whereas resting muscle is soft, flabby and presents little resistance to extension, the contracted muscle is hard, rigid and resists extension. It might be thought therefore, in agreement with Fick, that the essential feature in muscular activity consisted in a change in its elastic qualities, and that contraction involved the setting up of tension which could be used for approximating the ends against resistance, as *e.g.* in raising a weight and so doing work or, as in the isometric twitch, degenerating into heat as the contractile state passed away. The potential energy of a muscle in a state of contraction but prevented from shortening is represented

approximately by the expression $Tl/6$, where l is the length of the individual fibres and T is the tension produced. If a stimulated muscle were simply an elastic body like a spring under tension, the amount of work which it could do when suddenly released would be a constant amount and equal to the expression just mentioned. The best method of testing the power of a muscle to do work is to hinder its contraction by opposing it to the inertia of a mass, the mass being either a heavy fly-wheel or an equilibrated beam (Fig. 68). If a spring under tension were made to pull against such an apparatus, the amount of work it would do would be independent of the mass moved. In muscle, however, it is found that the amount of work done against a large mass is larger than that done against a small one. The essential factor involved here is the speed with which a muscle is allowed to shorten: the greater the speed of shortening, the less within limits will be the work done. In the case of human arm muscles the work does not approach its maximum value unless the contraction has been opposed by a

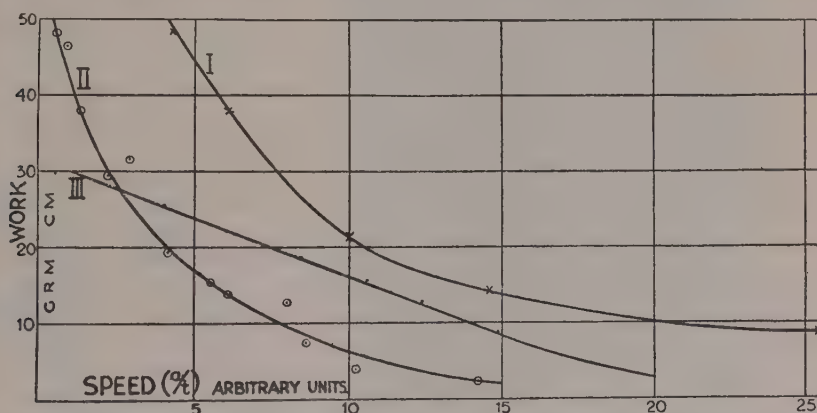


FIG. 69. Relation between Work done on Inertia Lever, and Speed of Shortening. Frog's sartorius muscles stimulated directly and isometrically with maximal tetanus, and released to work on lever only after maximal tension attained. Speed in arbitrary units, a/t , where a = amount and t = time of shortening.

mass large enough to make it occupy at least two seconds. The same relation is found in frog's muscle, the only difference being that the frog's muscle is ten times quicker than that of man.

The apparatus used in testing the relation of rate of shortening to work done is shown in Fig. 68. An equilibrated beam, the inertia lever, is a steel rod mounted on knife edges in the middle. By connecting the muscle to the rod at various distances from the centre and by mounting pairs of weights (W, W) upon the rod, an effect can be obtained equivalent to allowing the muscle to pull against a wide range of freely suspended masses. The weighted lever thus retards the shortening of the muscle by causing it to accelerate 'equivalent masses' of different sizes. A small rider (1 to 3 gms.) is hung on the lever, just sufficient to extend the muscle at rest. A thread from the muscle is connected to a quick-release mechanism, so that by an electro-magnet the muscle is allowed to exert its pull on the lever at any desired period after the beginning of its excitation. The diagram (Fig. 69) shows the relation between the work done on the inertia lever and the speed of shortening.

OPTIMAL RATE OF CONTRACTION. We have seen above that the slower the speed of shortening of a muscle the greater is the amount of work done. It must be remembered however that energy is required in order to *maintain* the contracted condition in muscle. As the contraction is prolonged there will be a greater expenditure of energy as well as a greater amount of work done. There will thus be a point at which the extra energy

required to maintain the contraction more than compensates for the gain in work done by increased duration of the contraction, so that for each group of muscles there will be an optimal rate at which the muscles will work with the greatest economy. We have seen that in the case of the human arm muscles the rate is ten times slower than in the isolated frog's muscle, and

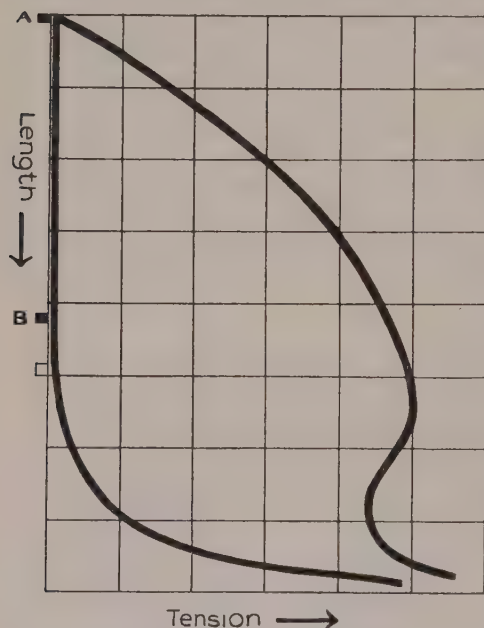


FIG. 70. Diagram to show the Relation between the Initial Length of a Muscle and the Tension developed in it during Excitation (as measured by the isometric method). The tension developed at each initial length is measured by the horizontal distance between the two thick lines, the left line representing the resting muscle, and the curved thick line on the right the contracted muscle. (From BLIX.)

greatest length work at a maximum mechanical disadvantage which lessens continuously as the muscles shorten and approximate their points of attachment. The load on a muscle is thus diminished continuously as the muscle contracts.

The relationship between initial length and the tension developed is shown in Fig. 70, which has been constructed from data given by Blix, who first pointed out this relationship. Moreover, as Lucas and A. V. Hill have shown, not only does increased initial tension, which of course would increase the length of the muscle, augment the tension set up during excitation, but it also prolongs the duration of the contractile stress.

Most of these results indicate that the change occurring in a muscle on excitation involves not only a change of tension but also a change in the viscosity of the contents of the muscle fibre. One may indeed, with Gasser and A. V. Hill, imagine these contents as undergoing a momentary condition of coagulation with the production of fibrils which tend to contract, but whose contraction is resisted by the increased viscosity set up by the formation of the fibrils themselves.

This double change in the contracting muscle is brought out very clearly by some experiments by Gasser on the results of a sudden partial release of the muscle under-

probably the rate will vary according to the mass of the limb involved and therefore, to a certain extent, to the size of the individual. It is a familiar experience that the effort of going upstairs becomes less as the rate is diminished, but not indefinitely, and that it may become more tiring if the rate is made too slow. The same thing applies to practically any form of exercise in which external work is being done.

EFFECT OF INITIAL LENGTH OF FIBRE. The tension developed in a muscle contracting isometrically in response either to a single stimulus or to a short tetanus is not constant but is found to vary with the initial length of the muscle. As the length of the resting muscle is increased by extending it up to a length somewhat greater than that which it possesses in its normal relations in the body, the tension developed on contraction also increases.

In the body the bony levers are so arranged that the muscles at their

going isometric contraction. The apparatus used is shown in Fig. 71. By means of an electric release mechanism, the muscle can be allowed to shorten to a measured extent at a moment when its tension resulting from stimulation is fully set up. The extent of the shortening allowed was determined by the knot K, which was caught in the lower

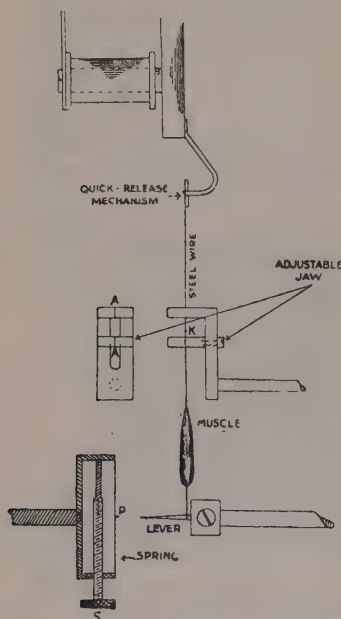


Fig. 71. Apparatus for allowing a sudden limited Shortening of a Muscle during its Isometric Contraction. (GASSER and A. V. HILL.)

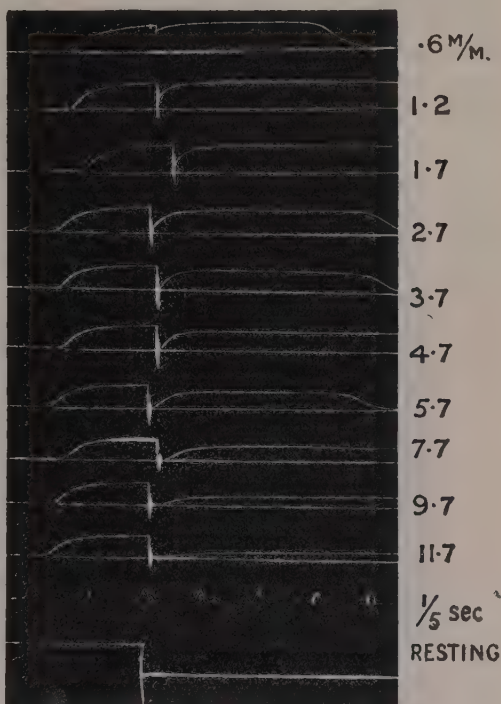


Fig. 72. Curves of Isometric Contractions during which a limited sudden Release was allowed. Right, amount of release allowed, mm. Bottom record, release of resting muscle. Read from left to right. (GASSER and HILL.)

limb of the adjustable jaw. It might be expected that under these circumstances the muscle thus partially released would at once take up the lower condition of tension associated with the smaller length of the fibres given it by the release. What one actually finds (Fig. 72) is that, on releasing the muscle, the isometric lever sinks right to the base line and then comparatively slowly rises to the new tension appropriate to the new length of its fibres. The explanation of this curve is that the instantaneous change in the elastic properties of the muscle cannot be followed at once by the viscous contents of the muscle fibres; and we notice that the rise of the lever after the release is almost identical with the first rise of the lever on the application of the stimulus. These curves can be imitated on a thin-walled rubber tube which is filled with a highly viscous fluid. We must therefore assume that when a muscle is stimulated two changes occur: (1) a sudden rise of tension, (2) a sudden increase in the viscosity of the contents of the fibres. The result

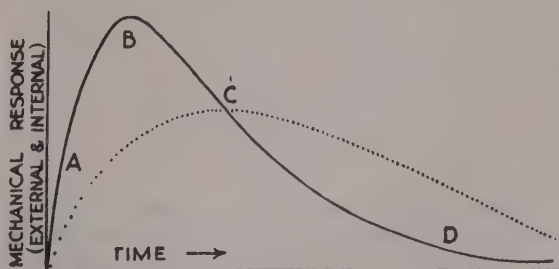


Fig. 73.

is to delay both the changes in form and the changes in tension of the contracting muscle. If it were not for this increase in viscosity, the contraction on stimulation might begin at the moment of stimulation itself, though it would always take a certain time to rise to its maximum. This double internal change in muscle is shown diagrammatically in Fig. 73. The unbroken line represents the sudden rise of tension and of viscosity beginning at the moment of stimulation. The external response, shown by the dotted line, will lag behind the internal change owing to the retarding effect of the viscosity change.

EFFECT OF TEMPERATURE ON THE MECHANICAL RESPONSE

Speaking generally, the effect of warming a muscle is to quicken all its processes. The chemical processes involved in the phase of shortening as well as those responsible for relaxation are hurried up, while the viscosity is diminished. The latent period therefore becomes shorter and the muscle curve steeper and shorter.

It is very often observed that in an isotonic twitch the height of contraction of the warmed muscle is greater than that obtained at ordinary temperatures. It seems that

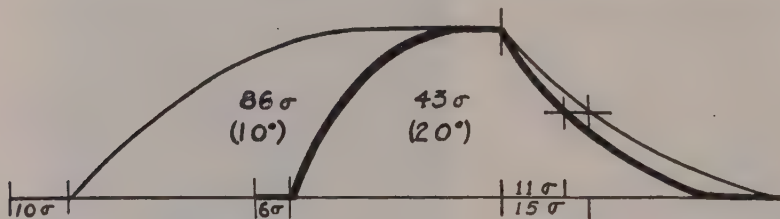


FIG. 74. Two Isometric Twitches from intact Gastrocnemius of Decerebrate Frog at 10° C. and 20° C. At 10° C. the latent period = 10 σ , and at 20° C. = 6 σ ; the contraction period at 10° = 86 σ and at 20° = 43 σ ; the times for half-relaxation were respectively 15 σ and 11 σ . (FULTON, "Muscular Contraction.")

this apparent increase in height is really instrumental in origin, the quicker moving muscle jerking the lever beyond the real extent of the contraction.

The question is however studied better on the muscle contracting isometrically. With efficient methods of recording it is then found, at any rate in the frog, (1) that the tension developed in a single twitch diminishes slightly as the temperature is raised from 0° C. to 25° C.; (2) that the tension developed in a tetanus lasting a sufficient time to attain its maximum is increased with rise of temperature, but not to a very marked extent; (3) that the durations of the latent period and contractile process are greatly reduced, and the duration of relaxation somewhat reduced by rise of temperature (Fig. 74).

If a muscle be heated gradually (without stimulation) up to about 45° C., it begins to contract slowly at about 34° C., and this contraction reaches its maximum at 45° C., at which point the muscle has entered into pronounced *rigor mortis*.

Cold has the reverse effect. The intramolecular processes which lie at the root of the muscular activity are slowed, so that the latent period and the contraction period are prolonged. The action of cold on the *excitability* of muscle is to increase it, so that any form of stimulus is more effective at 5° C. than at 25° C. If a muscle be cooled for a short time to zero or a little below, it loses its irritability, which returns if the muscle be gradually warmed again. Prolonged exposure to severe cold irrevocably destroys its irritability. Warming the muscle will now simply bring about *rigor mortis*.

FATIGUE

A muscle will not go on contracting indefinitely. If it be repeatedly stimulated, changes soon become apparent in the curve of contraction. The latent period is prolonged, as well as the length of the contractions; the absolute height and work done are diminished. At the same time the muscle does not return to its original length; the shortening which remains is spoken of as '*contraction remainder*.' After an initial rise during the first few contractions, these diminish uniformly in height till they are no longer apparent, so that the muscle is now said to have lost its irritability. At the same time there is a great prolongation of the relaxation, so that after forty or fifty contractions several seconds may elapse before the lever returns to the base line (Fig. 75).

If left to itself, the muscle which has been exhausted by repeated stimulation will partially recover. The recovery is hastened by passing a stream



FIG. 75. Muscle Curves showing Fatigue in consequence of Repeated Stimulation. The first six contractions are numbered, and show the initial increase of the first three contractions. (BRODIE.)

of blood, or even of salt solution, through the blood vessels of the muscle. Still more important is a free supply of oxygen.

The phenomena of fatigue depend on two factors :

(1) The consumption of the substances available for the supply of potential energy to the contractile material.

(2) The accumulation of products of the contractile process. Among these waste products the lactic acid is of greatest importance. Fatigue may be artificially induced in a muscle by 'feeding' it with a dilute solution of lactic acid, and again removed by washing out the muscle with normal saline solution containing a small percentage of alkali. The beneficial effects of oxygen supply are due to the removal of lactic acid.

THE ACTION OF SALTS

The action of sodium salts on muscle is of considerable interest. We are accustomed to use a 0.65 per cent. solution of NaCl as a 'normal fluid' to keep frog's muscle preparations moist. If however the solution be made with distilled water, it has a distinctly excitatory effect upon the muscle, so that single induction shocks may cause tetaniform contractions. The same excitatory effect is still better marked with solutions of Na_2CO_3 . If a thin muscle, such as a frog's sartorius, be immersed in a solution containing 0.5 per cent. NaCl , 0.2 per cent. Na_2HPO_4 , and 0.04 per cent. Na_2CO_3 (Bieder-

mann's fluid), the muscle enters into a series of frequent contractions, so that it may wriggle from side to side, or may even 'beat' for a time with regularity.

This excitatory action of sodium salts is neutralised by the addition of traces of calcium salts. Hence the normal saline used in the laboratory should always be made with tap water, containing calcium salts. But it is better to use Ringer's solution.

Potassium salts, although forming so important a constituent of the ash of muscle, act as muscle poisons, quickly and permanently destroying its irritability. If a muscle be transfused with normal fluids containing minute traces of potassium salts, it at once shows all the signs of fatigue, signs which may be removed by washing out the potassium salts by means of 0.65 per cent. NaCl solution. It is possible that the setting free of potassium



FIG. 76. A. Tracing of the Contraction of a Frog's Sartorius, poisoned with veratrine, in response to a momentary stimulus. The time-marking indicates seconds.

B. Tetanic Contraction of Normal Sartorius in response to rapidly interrupted stimuli. (The duration of the stimulus is indicated by the words 'on' and 'off.')

It will be noticed that the two curves are practically identical. (Miss BUCHANAN.)

salts may be one of the factors involved in the development of the normal fatigue of muscle.

If a frog's muscle be isolated and kept moist for a few hours, it often shows a complete loss of excitability, but regains it after a short immersion in Ringer's fluid, and does not become non-irritable again during its survival. The cause is unknown.

THE ACTION OF DRUGS

Of the drugs that have a direct action on muscle, the most remarkable is veratrine which causes an excessive prolongation of a muscular contraction (produced by a single stimulus). Thus the 'twitch' of a muscle poisoned with veratrine may last fifty or sixty seconds, instead of the normal one-tenth of a second (Fig. 76).

Barium salts have a similar though less marked effect.

In order to carry out the poisoning with veratrine, very weak solutions (1 in 100,000 or 1 in 1,000,000 of normal saline) should be used and the muscle exposed to its action for some time. We get then on a single stimulus a response lasting many seconds and exactly similar in height and form to a tetanus obtained by discontinuous stimulation. If stronger solutions be used, the action of the drug is apt to affect the fibres unequally, so that we may have a sharp normal twitch preceding the prolonged contraction. If the muscle be excited several times immediately after the prolonged contraction has passed away, it responds with twitches like those of a normal muscle; but if allowed to rest a few minutes, stimulation is again followed by the peculiar long-drawn-out contraction.

THE CHEMICAL AND THERMAL CHANGES WHICH ACCOMPANY ACTIVITY

The principle of the conservation of energy teaches us that the energy of the contraction of muscle must be derived from chemical changes, probably

processes of decomposition and oxidation, occurring in the muscle itself. In seeking out the nature of these changes three methods are open to us :

(1) We can examine the changes in the muscle itself.

(2) We can investigate the changes in the medium surrounding the muscle. Muscle may be exposed in a vacuum or in a confined space of air, and its gaseous interchanges during rest and activity compared. Or we may lead a current of defibrinated blood through excised muscles, and determine the change in the composition of the blood in passing through the muscle under various conditions.

(3) A method, which although apparently complex has rendered the utmost service to the physiology of muscle, is to use the changes in the total metabolism of the animal during rest and muscular work as a clue to the muscular metabolism itself. In such a case the respiratory exchanges of the animal are determined (viz. its oxygen intake and its CO_2 output), and the urine and fæces are carefully analysed, in order to judge of the action of muscular work on the carbon and nitrogen metabolism of the body.

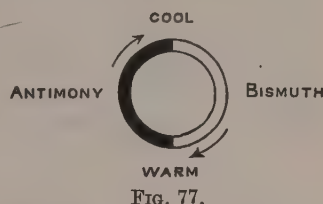
We may begin by dealing with the evidence afforded by the first two methods of investigation and then see how far our conclusions are borne out by experiments on the respiratory exchanges of the whole animal. Chemical investigation however can yield but limited information as to the course of events occurring during the phases of contraction, relaxation and recovery. All we can do is to examine the summated results of a long series of contractions. A single twitch will give no detectable chemical change. On the other hand every chemical change is associated with production or absorption of heat, and our methods for detecting small differences of temperature are so exact that we are able to measure not only the heat production during a single twitch but also the time-course of its evolution, and are thus in a position to assign the different chemical events to the appropriate phase of muscular activity.

The experience of everyday life teaches us that muscular exercise is associated with increased production of heat. In large animals the production

of heat in muscular contraction can be easily shown by inserting the bulb of a thermometer between the thigh muscles, and stimulating the spinal cord. The rise of temperature produced in this way may amount to several degrees. This observation is confirmed when we investigate the contraction of an isolated muscle outside the body. If a frog's muscle is tetanised, its temperature rises from 0.14° to 0.18°C. , and for each single twitch from 0.001° to 0.005°C.

FIG. 78A. Plan of Construction of Thermopile. (HARTREE.)

Such small changes in temperature as 0.001° cannot be estimated by ordinary thermometric methods. By converting a heat change into an electrical change however we can estimate differences of temperature with much greater accuracy and fineness than by the use of a thermometer. The principle employed in measuring temperature by electrical methods depends on the fact that, when the junctions of a circuit made of two metals are at different temperatures, a current of electricity generally flows through the circuit. This current can be measured



by means of a galvanometer, and is proportional to the difference of temperature between the two junctions. Thus in the circuit (Fig. 77) composed of two metals, antimony and bismuth, if the upper junction be cooled, there will be a current flowing from antimony to bismuth in the direction of the arrow, and this current will within limits be proportional to the difference of temperature.

To measure the rise of temperature in a muscle during its contraction, the thermopile is made in the form of a grid. It consists of forty or more turns made with alternate segments of fine iron and constantan wire soldered together with silver solder and wound between the arms of a U-shaped frame of glass (Fig. 78A) so that

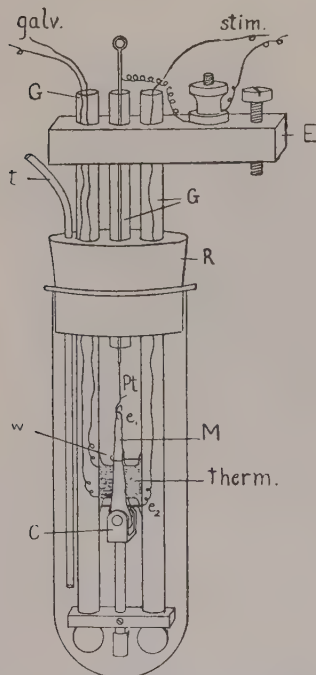


FIG. 78B. Arrangement of Thermopile and Muscle for measuring Heat Production during Contraction. E is an ebonite block by which the whole apparatus is secured upright in the water bath; *w* is a platinum wire guide for the muscle to insure good contact with the thermopile; *t* is a fine glass tube through which Ringer's solution or oxygen can be introduced into the chamber; C is an ebonite clamp to hold the muscle; it is secured to the glass rods by means of an ebonite bar at the base and a silver-plated set screw. (W. O. FENN.)

two sets of junctions lie half-way between the arms of the U and the other two sets on the outside edges of these arms. A slip of mica is inserted between the front and back parts of the spiral, and the wire insulated throughout with a coating of shellac varnish. Another method is to wind the whole spiral with constantan wire and to silver-plate alternate segments so that the junctions (between silver and constantan) come just where required. A pair of muscles (*e.g.* sartorii) is used, and is arranged so as to straddle the grid, each muscle lying close against the middle junctions, while the outer junctions are maintained at a constant temperature. For this purpose the arrangement shown in Fig. 78B may be used. Through the rubber stopper, R, of a large test tube pass three glass tubes, G. Between these the thermopile is fastened by means of shellac. The leads from the thermopile to the galvanometer pass through two holes in one of the glass tubes. The muscle is stimulated by the electrodes e_1 and e_2 . The lower electrode e_2 is connected with the stimulating circuit by means of a copper wire leading up through the other glass tube. The upper electrode e_1 consists of an 8-shaped loop of platinum tied between the two muscles, and soldered to a fine steel rod, which makes electrical connection with the stimulating circuit, and mechanical connection with the lever which records the contractions of the pair of muscles. The whole apparatus is sunk well beneath the surface of the water in a Dewar flask, which is stirred by a continuous current of air. The leads from the thermopile are taken to a very sensitive galvanometer of low resistance, carefully shielded from disturbing effects of electrical circuits in its surroundings.

The thermopile and galvanometer can be calibrated so that the changes of temperature in the muscle may be deduced directly from the galvanometer excursions. In order to convert these temperature changes into amounts of heat actually evolved, the muscle at the end of the experiment is killed, and

the heating effect observed of passage of an interrupted current. Knowing the strength of the current and the resistance of the dead muscle, the exact amount of heat required to produce an observed deflection can be calculated.

Calorimetric Method. For the determination of the total heat production in a muscle or group of excited muscles over a considerable time we may use the micro-calorimeter devised by A. V. Hill and R. A. Peters.

Two small Dewar flasks of about 120 c.c. capacity are used (Fig. 79). In each of these are suspended four frogs' muscles immersed in about 50 c.c. of Ringer's fluid. They are arranged so that their nerves can be stimulated while in the flask. Thermojunctions are immersed in the fluid in the two flasks. In this arrangement the heat

loss or gain in the two vessels should be identical. Any difference of temperature between the two vessels as revealed by the galvanometer is therefore due to liberation of heat in the muscles which are being excited. The same arrangement may be used for studying the heat production in a muscle as it gradually undergoes rigor.

We have seen that an isolated frog's muscle can give a normal contraction in the entire absence of oxygen—it may be in a vacuum or immersed in pure nitrogen or hydrogen gas. Under these conditions there is no increased *production* of carbon dioxide associated with contraction. If a series of stimuli be given to the muscle, it continues to give single contractions which gradually diminish in height until the muscle is completely fatigued and will give no further response to the strongest stimulation. At this point if the muscle be cut up in ice-cold alcohol, it is found to contain about 0.2 per cent. lactic acid. A fresh muscle contains only the merest trace of this substance.

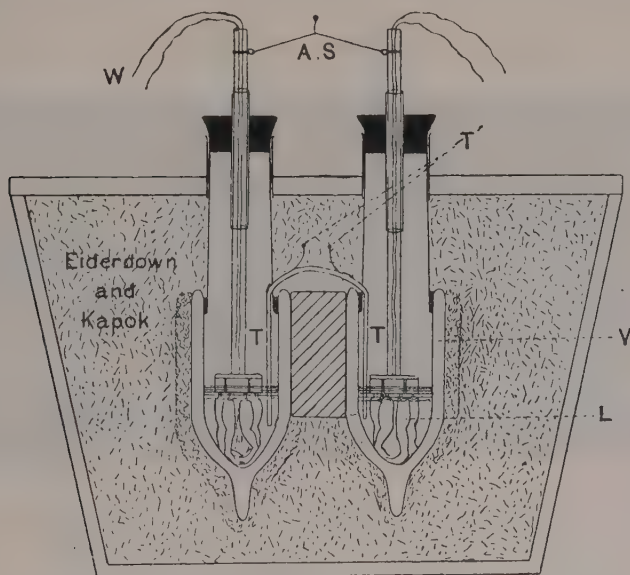


FIG. 79. Arrangement of two Dewar Flasks for studying the Production of Heat in Muscles over a considerable period of time. (R. A. PETERS.)

At the same time, if comparative experiments be carried out on a number of muscles, it is found that the appearance of lactic acid is associated with a corresponding diminution in the glycogen content of the muscle. If the muscle after complete fatigue be kept until it undergoes rigor, or if this state be induced by the action of chloroform vapour, it is found to contain 0.4 per cent. lactic acid. This is the principal chemical change which can be proved to take place during muscular contraction, namely, the conversion of glycogen to lactic acid. It has been shown that there is no decisive change in the fat content or in the nitrogenous constituents of the muscle under these conditions. The essential factor of contraction is thus similar to that occurring during rigor, the change during rigor however being more extensive. In rigor the muscle is dead, no recovery being possible. If a thin muscle, such as the frog's sartorius, after complete fatigue in an atmosphere of nitrogen, be exposed to pure oxygen (in order to facilitate the penetration of this gas to all parts of the muscle), the muscle rapidly recovers, so that on stimulation it will give a further series of con-

tractions; and in oxygen this process of fatigue and recovery can be repeated many times (Fig. 80). When sartorius muscles are made to contract in oxygen, a distinct production of carbon dioxide is found to follow each period of activity, and careful experiment has shown that this evolution of carbon dioxide is associated with the disappearance of an equal volume of oxygen. During the process of recovery from fatigue in oxygen, the lactic acid which has accumulated is found to disappear.

The obvious interpretation of these chemical data is that contraction is associated with the conversion of glycogen into lactic acid, the sudden appearance of the latter substance at certain interfaces of the muscle structure being responsible for the mechanical change following excitation. Relaxation must be due to a removal of the lactic acid by diffusion away from the active surfaces or by neutralisation. The process of recovery seems to be associated with the oxidative removal of the lactic acid previously produced. But a muscle can be fatigued and allowed to recover several times in oxygen. If at the end it be allowed to undergo rigor, it is found to con-

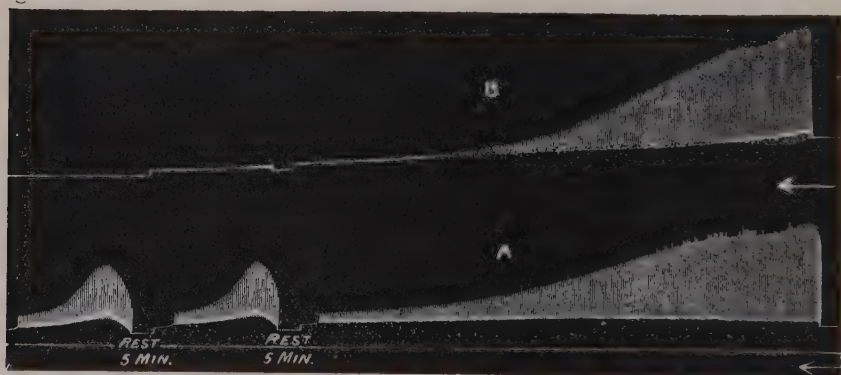


FIG. 80. Fatigue in a Pair of Sartorii. (FLETCHER.)
 Max. break shocks one per second. Load 6 grammes. Temp. 19° C.
 A. Exposed to oxygen. B. Exposed to nitrogen.

tain just the same amount of lactic acid as if it had not contracted at all. If all the lactic acid produced during contraction were removed by oxidation in the process of recovery, one would expect finally to obtain a smaller lactic acid production during rigor. These results suggest that the process of recovery involves, not a complete oxidation of the lactic acid previously produced, but the oxidation of a part only of this substance, the rest of the lactic acid being reconverted to glycogen in the muscle, so that it is replaced in a position in which it can undergo reversion and be available for the production of the energy of further contractions.

The final decision on these questions has been given by the work of A. V. Hill and his pupils on the heat production during muscular contraction. By the calorimetric method it may be shown that in anaerobic muscular contractions the formation of 1 gramme of lactic acid is attended with the evolution of 370 calories. This heat does not come off at once but in two phases, there being an evolution of heat immediately following on excitation, and a subsequent evolution of heat accompanying relaxation. In Fig. 81 the dotted line shows the course of contraction recorded isometrically. (The contraction is prolonged because it is taken from the muscle of a toad at 0° C.) Two galvanometer curves are given, the control being

that produced by warming the dead muscle electrically, the observed one being that obtained when the live muscle was stimulated to give a single twitch. Analysis of the observed curve gives the exact course of the heat production during the contraction (shown by the stepped curve). It will be seen that there is a sudden burst of heat production immediately following excitation, and then a somewhat smaller production of heat accompanying relaxation. It is inferred that the first burst of heat production is due to the conversion of glycogen into lactic acid, while the second is due to the reaction of lactic acid with the muscle substance, ending in its neutralisation. In this neutralisation the inorganic salts of the muscle take but a small part, the chief rôle in the process being played by the proteins of the

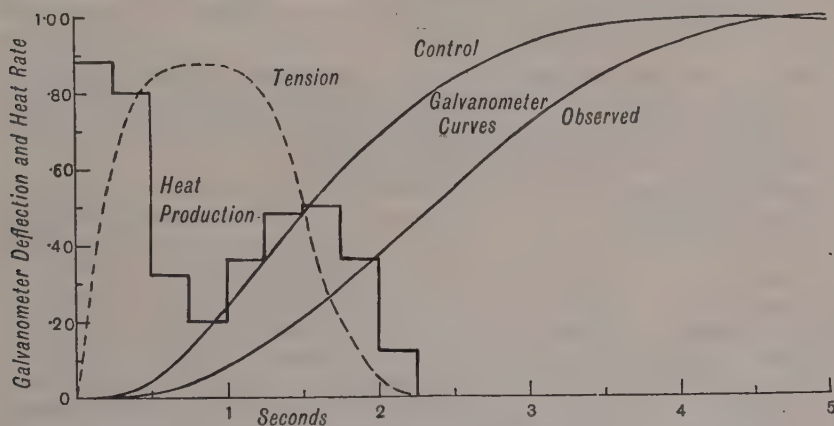
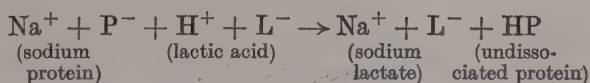


FIG. 81.—Course of Heat Production in a Single Twitch. (HARTREE.)

muscle, which exist as ionised compounds of protein and alkali—potash or soda—as in the following equation :



We may make the following balance-sheet for the anaerobic contraction of muscle :

	Cals.	Cals.
Total energy in anaerobic muscular activity per 1 gramme of lactic acid produced (Meyerhof)		370
Heat of combustion of dissolved glycogen (Slater)	3836	
Heat of combustion of dissolved lactic acid (Meyerhof)	3601	
Heat of formation of lactic acid from glycogen	235	
Heat of neutralisation of lactic acid by sodium protein of muscle (Meyerhof)	135	
	370	370
Balance left for other chemical processes		Nil.

During recovery in oxygen there is a further prolonged evolution of heat. As this amounts but to a further 370 calories per gramme of lactic acid produced, only a small part of the lactic acid can undergo oxidation to CO_2 , since oxidation of 1 gramme of this substance involves the liberation of 3600 calories; and we must conclude, as suggested above, that

the greater part of the lactic acid is reconverted, during recovery, into glycogen. As a matter of fact, only about one-fifth of the lactic acid undergoes complete oxidation, part of the energy of this oxidation appearing as heat and being measured by the thermopile, while the rest of it is absorbed in the endothermic reversion of lactic acid into glycogen. It seems probable that the change from glycogen to lactic acid during contraction is similar to that taking place during rigor and that a hexose phosphate occurs as an intermediate product.

The rôle of phosphates in muscular contraction has been brought to the foreground by the discovery, made simultaneously by Fiske and Subbarow and by P. and G. P. Eggleton, of a compound of creatine and phosphoric acid, which has been named Phosphagen by the Eggletons. When lactic acid is formed, phosphagen is broken up into creatine and free phosphoric acid, and the latter compound may thus become available for conversion into hexose phosphate.

When we turn to experiments on the whole animal (and for this purpose experiments on man are to be preferred) we obtain a striking confirmation of the views as to the intimate nature of muscular activity which have been derived from experiments on isolated frog's muscles.

The total energy of the body is derived ultimately from the oxidation of foodstuffs. The products of this oxidation are excreted partly with the urine, partly with the expired air, so that examination of these excretions, combined with a measurement of the oxygen taken into the body in respiration, serves as a measure of the total oxidations occurring in the body. Many experiments on the effect of bodily exercise have shown that the excretion of nitrogenous substances is not immediately affected, while on the other hand the slightest change in the amount of muscular activity is revealed at once by a corresponding alteration in the respiratory exchanges. When a man runs he becomes, as we say, 'out of breath,' and this increased respiration is associated with an increased intake of oxygen and excretion of CO_2 . We must conclude therefore that the main source of muscular energy is the oxidation of carbon: whether in the form of carbohydrate or of fat we shall have to discuss shortly.

A man at rest absorbs from the respired air about 300 c.c. oxygen per minute, and gives out about 250 c.c. CO_2 . The proportion of CO_2 given out to oxygen absorbed is called the 'respiratory quotient,' and its absolute amount depends on the nature of the foodstuffs or constituents of the body which are undergoing oxidation. If these were entirely carbohydrate, the respiratory quotient CO_2/O_2 would be equal to 1, as is apparent from the equation of oxidation of sugar:



When fats undergo oxidation, part of the oxygen taken in is used for the oxidation of the hydrogen, so that it does not appear in the expired air as CO_2 . If fats alone were being utilised, the respiratory quotient would be 0.71; with proteins alone, the respiratory quotient would be 0.81. Thus in herbivora, where the food is predominantly carbohydrate, the respiratory quotient approaches 1; in man, on a mixed diet, the respiratory quotient at rest is somewhere about 0.85.

Even the mildest form of exercise increases the intake of oxygen and output of CO_2 . Thus, in one experiment, walking at 3.5 miles per hour raised the oxygen intake from the resting value of 292 c.c. per minute to 1155 c.c. per minute. Under these circumstances there is very little change in the respiratory quotient, which was 0.85 during rest and 0.84 directly after exercise. With increased intensity of muscular exercise the intake of oxygen

may rise enormously, even to 3000 c.c. or in athletes to even 4000 c.c. per minute. A well-trained man can continue to run without getting further distressed while he is using 3500 c.c. oxygen per minute. On ceasing exercise the increased pulmonary ventilation rapidly falls, and after five to ten minutes the respiration and the oxygen intake have returned nearly to their previous amounts. When exercise can be maintained indefinitely, the processes of recovery in the muscles are keeping pace with the processes of contraction, *i.e.* the lactic acid that is formed during contraction is being steadily oxidised and replaced in its position as glycogen, so that there is little chance for accumulation of this substance either in the muscles or in the blood bathing the muscles. The fact however that the increased respiration continues for a few minutes after cessation of the exercise instead of falling at once to its previous resting value, shows that there is a certain lag in the oxidative processes of recovery; and further evidence for this lag is given by the fact that there is a small accumulation of lactic acid in the blood which must have come from the contracting muscles. Thus in the experiment just quoted, in which the subject was walking three and a half miles an hour, the lactic acid in the blood increased from 20.9 milligrammes per 100 c.c. during rest to 56.6 milligrammes per 100 c.c. one minute after exercise; and the amount of lactic acid in the blood directly after exercise is found to be proportional to the increased intake of oxygen above the resting amount after cessation of exercise.

So far we have considered only exercise which can be continued more or less indefinitely. The maximum severity of this exercise depends on the training of the individual, and physiologically on the extent to which his circulatory system and lungs can provide the working muscles with oxygen in proportion to their needs. The maximum intake of oxygen which, even in an athlete, can be carried by the blood and pumped round by the heart to the muscles is about 4000 c.c. Much severer forms of exercise are however possible than would be met by such an oxygen supply. In the ten or eleven seconds occupied in a 100 yards' sprint, the oxygen intake can be but little above the resting level. Immediately after completing the course the man pants violently and in the next few minutes will take in an excess of 4 litres of oxygen. During these eleven seconds the man's muscles have been contracting practically anaerobically, with the result of a considerable production of lactic acid. The oxidative removal of this lactic acid has been postponed to the end of the race. The man has thus 'gone into debt' for oxygen, and the extent to which he can run into debt depends on the amount of lactic acid which can accumulate in the working muscles without stopping their activity. After any severe form of exercise this oxygen debt is apparent. The highest amount which has been observed by A. V. Hill was 19 litres. Of course this accumulation of lactic acid in increased concentration in the contracting muscles causes increased diffusion of this substance out into the blood, from which some may also escape into the urine. The extent of the accumulation in the blood is shown in the accompanying diagram (Fig. 82.) It will be noted that the lactic acid which has accumulated in the muscle during the severe bout of exercise continues to escape when the exercise comes to an end, so that for the first few minutes its percentage amount in the blood first rises and then falls steadily. Most of this lactic acid passes back into the muscles, both the inactive muscles and those which have been active. In the muscles the process of oxidative recovery takes place, about one-fifth of the lactic acid being oxidised, while the other four-fifths is reconverted into glycogen. A certain amount may be converted in other tissues of the body, such as the liver, back into sugar, which is then

carried round by the blood to restore the glycogen supply of the muscles. The high oxygen debt which can be incurred, especially when breathing oxygen, shows that very considerable quantities of lactic acid may accumulate in the active muscles under these circumstances: thus a debt of 19 litres of oxygen would be equivalent to 133 grammes of lactic acid, *i.e.* to nearly 0.4 per cent. lactic acid in the contracting muscles.

Though moderate exercise, such as gentle walking, does not alter the respiratory quotient, very considerable alterations are brought about by severe exercise. We have seen that the lactic acid produced as a result of stimulation is neutralised during relaxation by interacting with the alkali proteins existing in the muscle. Although these proteins act as buffers,

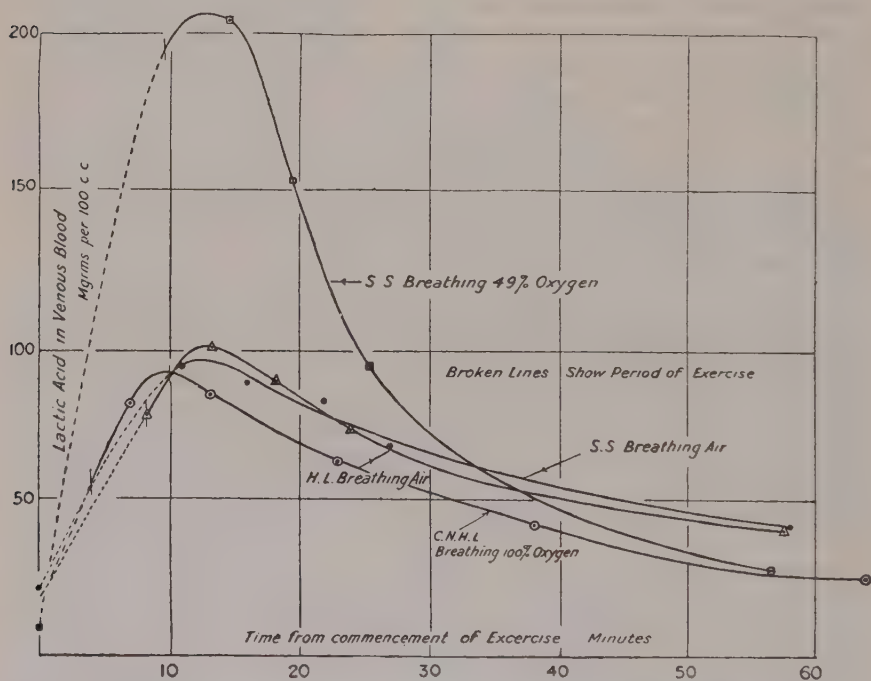


FIG. 82. Lactic Acid in Human Blood after severe Muscular Exercise.

Two experiments in air—one in 49 per cent. oxygen, one in 100 per cent. oxygen.

Note that the recovery process is not quite complete at the end of the time shown in the diagram. (HILL, LONG and LUPTON.)

minimising the change in reaction, *i.e.* in eH , of the tissues caused by the sudden appearance of an acid body, nevertheless some change must occur as the alkali protein is converted into deionised protein. This will increase the eH of the blood, and therefore will stimulate the respiratory centre. Such a stimulation is necessary for the increased intake of oxygen for the supply of the working muscles, but it has also the effect of quickening the elimination of CO_2 . Moreover the escape of lactic acid into the blood will drive out carbonic acid from this fluid and will increase its elimination by the lungs. Thus an amount of carbon dioxide would be eliminated by the lungs in excess of that produced by the metabolism of the body. For example, if the true metabolism during exercise were: oxygen 3 litres per minute, CO_2 2.4 litres per minute, the true respiratory quotient would be 0.8. If however 3 litres extra of carbon dioxide were displaced by the entry

of lactic acid into the blood and tissues, and this was eliminated in ten minutes, the apparent respiratory quotient would be raised to 0.9. This rise of CO_2 output and of respiratory quotient would be the initial event in any steady form of exercise, so that the increased breathing would be more marked while this extra CO_2 was being eliminated. After its elimination the organism enters into a "steady state": the excessive breathlessness disappears, and the individual can now go on running steadily for a long time, having attained the condition known as 'second wind.' With severe exercise of short duration, when a considerable oxygen debt is incurred, the escape of lactic acid into the blood causes a great dyspnoea immediately after the exercise, with a large output of CO_2 . The apparent respiratory quotient under these circumstances may rise to 1.5 or even to 2 (cf. Fig. 83). During the process of recovery the lactic acid is gradually removed and the excess CO_2

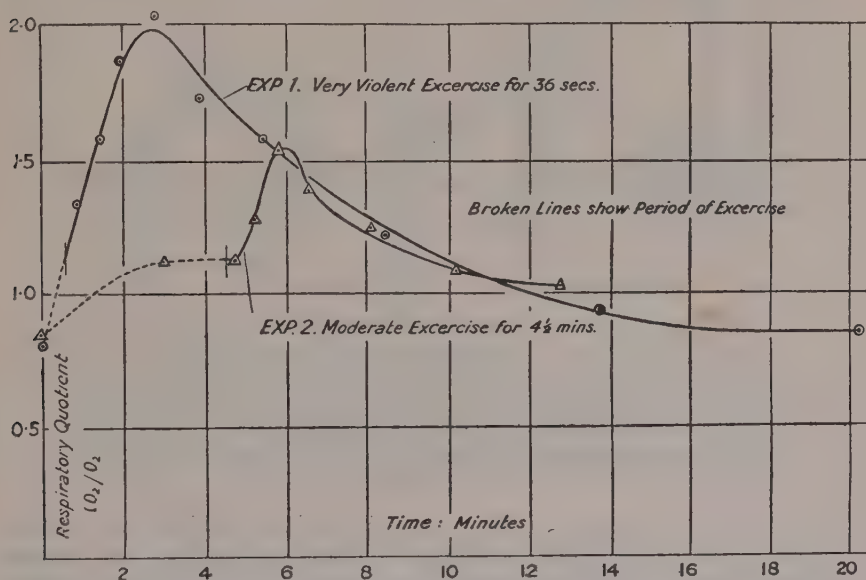


FIG. 83. The Respiratory Quotient during and after Muscular Exercise. These figures show the initial phase of recovery only. (HILL, LONG and LUPTON.)

which has been given off from the body is once more retained. We shall therefore expect to find a very large respiratory quotient immediately after heavy exercise, followed later on by a long lasting fall of the respiratory quotient below the resting level. If we make due allowance for these fluctuations in the respiratory quotient, due to the initial driving off of the CO_2 and its subsequent retention as the lactic acid disappears, we find that the corrected respiratory quotient of the exchanges, directly due to muscular exercise of short duration, is about unity, *i.e.* identical with that observed in the isolated frog's muscle (Fig. 84). We are therefore entitled to conclude that in the whole animal, as in the isolated frog's muscle, the energy of muscular contraction is derived in the first place from the breakdown of glycogen into lactic acid, but ultimately from the oxidation of lactic acid, or at any rate of a carbohydrate, to CO_2 and water.

Prolonged exercise will deplete the carbohydrate stores of the body, so that we may get later secondary changes in the respiratory quotient due, not directly to the muscular exercise, but to the necessity of replacing the diminished stores of carbohydrate by the conversion of protein or fat. These

subsequent changes in the metabolism of the body as a whole we shall have to consider more fully in a later chapter.

The carbohydrate stores of the muscles can be brought to a low level by a diet consisting almost entirely of fat, and containing no carbohydrate.

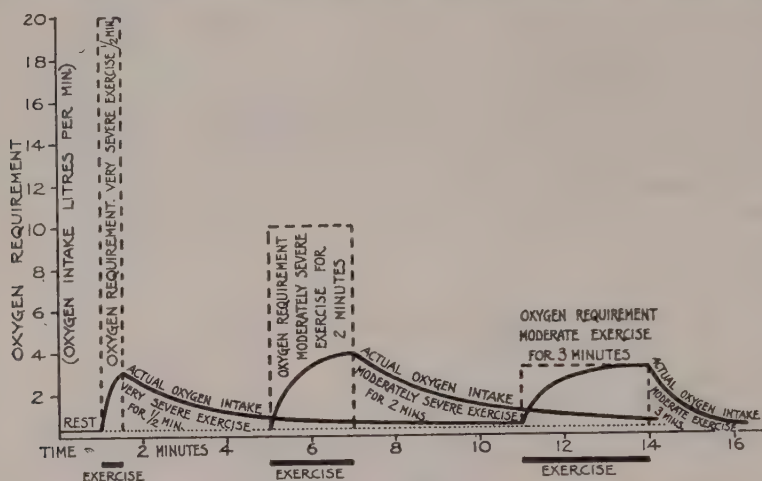


FIG. 84. Diagram to illustrate the Meaning of 'Oxygen Requirement,' and the Distinction between 'Oxygen Requirement,' and 'Oxygen Intake.'

The area of an oxygen requirement rectangle is, by definition, the same as that of the complete oxygen intake curve, each being measured from the level of the resting oxygen intake (shown dotted). Three periods of exercise of different severity. When the CO_2 output is measured over the same period of time, it is found (after subtraction of the resting output) to be equal to the oxygen intake, i.e. the R.Q. of the excess respiratory exchanges due to the muscular exercise, provided this be of short duration, is equal to 1.

After three days of such a diet the subject is disinclined for exercise and easily susceptible to fatigue. Control experiments on animals show that under these conditions the glycogen content both of muscles and liver is minimal. But experiments by Furusawa have proved that

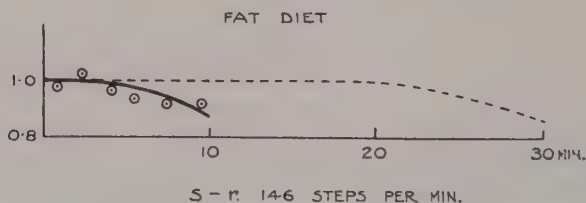


FIG. 85. The Respiratory Quotient of the Gaseous Metabolism of Muscular Exercise in a Subject on a Fat Diet (thick line) compared with that of a Subject on a Normal Diet (dotted line). The exercise was 'standing running' at 146 steps per minute. (FURUSAWA.)

even after the R.Q. has been reduced to 0.75 by such a diet, the complete cycle of exercise and recovery has a respiratory quotient of unity provided that the exercise be not too long. As the duration of the exercise is increased, the R.Q. falls rapidly to the low value observed in the normal individual only after prolonged periods of hard exercise (Fig. 85).

ELECTRICAL CHANGES IN MUSCLE

If a current from a battery be passed between two plates of platinum immersed in acidulated water or salt solution, *electrolysis* of the water takes place, bubbles of oxygen appearing on the positive plate (anode), and bubbles of hydrogen on the negative plate (cathode). If now we remove the battery, and connect the two plates (electrodes) by wires with a galvanometer, a current passes through the galvanometer and water in the reverse direction to the previous battery current. This current is called the polarisation current, and is due to the electrolysis of the water that has taken place. The vessel in which the electrodes are immersed has in fact become a storage cell, the platinum covered with oxygen bubbles being the positive *element*, and that covered with hydrogen bubbles the negative *element*. Exactly the same process of electrolysis or polarisation takes place when we pass currents through the tissues of the body by means of metallic electrodes.

Hence before we can study accurately the electrical changes that occur normally in

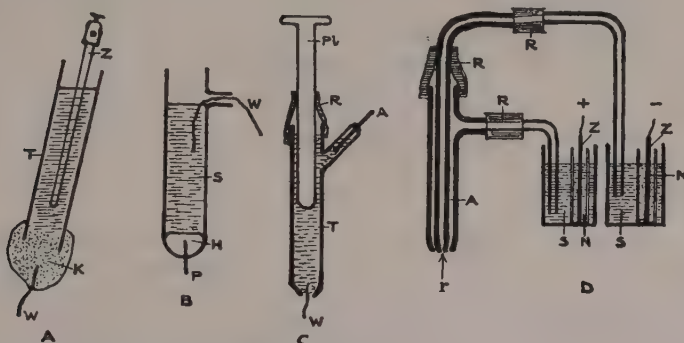


FIG. 86. Types of Non-polarisable Electrodes.

(A) Noyons' type of non-polarisable electrode. Z = amalgamated zinc rod imbedded in 10 per cent. gelatine containing ZnSO_4 , and contained in the glass tube, T. K = plug of kaolin made with isotonic NaCl solution. W = thread wick soaked in isotonic NaCl solution leading to tissue.

(B) Ostwald type of N.P.E. P = platinum wire making contact with mercury H. S = isotonic NaCl solution containing solid calomel. W = saline wick lead to tissue.

(C) Lapique's AgCl electrode. A = silver electrode coated with AgCl. Pl = plunger fitting rubber sleeve R, for filling electrode with NaCl solution. W = saline wick lead.

(D) Pratt's pore electrode. r = the fine pore which is the stimulating point. The tube is filled with saline solution and connected with the saline solution in the vessel S, in which is a porous N.P.E. cell filled with ZnSO_4 solution and having a Zn rod immersed in it. The outer tube, A, is the other electrode and is similarly connected with the other N.P.E. cell. R = rubber connections. (From "Recent Advances in Physiology.")

living tissues, it is necessary to have some form of electrodes in which this polarisation will not occur.

With one exception, polarisation always results when a current passes from an ordinary metallic conductor to a saline solution, but not when it passes from one saline solution to another. This exception is when the metal dips into a solution of its own ions, and this fact is taken advantage of in the construction of *non-polarisable electrodes*. In these a metal dips into a solution of its salt; any tendency for polarisation is at once counteracted at the cathode by deposition of the metal on to the electrode from the solution, or at the anode by solution of the metal of the electrode to neutralise the negative charges carried thence by anions. Some types of these electrodes are shown diagrammatically in Fig. 86.

In such electrodes the conduction of the current through the nerve or muscle to the metallic part of the circuit may be represented as shown in Fig. 87.

If a muscle such as the sartorius be removed from the body, and two non-polarisable electrodes connected with a delicate galvanometer be applied to two points of its surface, there will often be a deflection of the mirror

attached to the galvanometer, showing the presence of a current in the muscle from the ends to the middle, and in the external circuit from the middle (or equator) to the ends. It was formerly thought that this current was always present in all normal muscles, but it has been conclusively shown that this current of resting muscle is due to the excitatory effects of injury. The less the preparation is injured, the smaller is the current to be obtained from it. Hermann described the fact of the existence of currents of rest thus: "In partially injured muscles every point of the injured part is negative towards the points of the uninjured surface." Fig. 88 shows the direction of the current in a muscle with two cut ends. When the injured

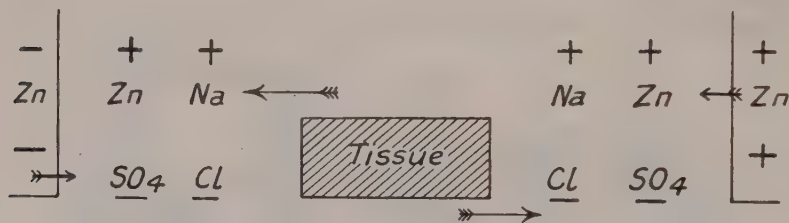


FIG. 87.

fibres are quite dead, this current of rest or 'demarkation current' disappears. The current is due to the electrical differences at the junction of living and dying (not *dead*) tissue. If the sartorius of the frog be cut out and immersed for twenty-four hours in 0.6 per cent. NaCl solution made with tap water (*i.e.* containing calcium), all the injured fibres die, and the uninjured fibres are then found to be iso-electric and therefore currentless.

If one end of the muscle be now injured by cutting or burning, a galvanometer will show the presence of the current of injury, or demarcation current between injured and uninjured tissue. The existence of this current may be demonstrated without using a galvanometer. If the nerve of a sensitive

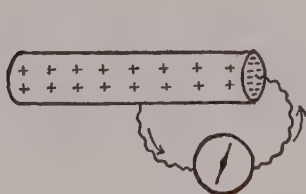


FIG. 88. Current of Rest.

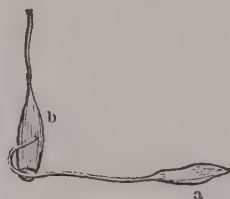


FIG. 89. Rheoscopic Frog.

muscle-nerve preparation *a* (Fig. 89) be allowed to fall on an excised muscle *b*, so that one point of the nerve is in contact with the cut end and one with the surface of the second muscle *b*, the muscle *a* will contract each time the nerve touches *b* so as to complete the circuit. If the nerve of *b* is tetanised, *a* as well as *b* enters into a tetanic contraction, for reasons that will be clear later.

Although resting uninjured muscle shows no current, there is no doubt that whether injured or not, a very definite electrical change occurs in it when it contracts. To show this change, we may lead off two points, one on the cut end and one on the surface of the muscle of a muscle-nerve preparation, to a galvanometer. We shall first obtain a deflection of the mirror of the magnet, due to the demarcation current. If now the nerve be stimulated with an interrupted current so as to throw the muscle into a

tetanus, the ray of light from the galvanometer mirror swings back towards the zero of the scale, showing that the current which was present before is diminished. When the excitation of the nerve is discontinued, the galvanometer indicates once more the original current of rest. This diminution of the current of rest during activity of a muscle is spoken of as the 'negative variation.'

In carrying out this experiment it is usual to compensate the demarcation current by sending in a small fraction of the current from a constant cell. The arrangement of the apparatus is represented in the accompanying diagram. Two non-polarisable electrodes *np* are applied to the surface and cross section of a muscle *m*. These are connected with the shunt of the galvanometer, one of the wires however being connected with a Pohl's reverser *p*, and this in its turn with the shunts. The two end terminals of the reverser are connected with a potentiometer, through the wire of which, *ab*, a constant current is passing from the Daniell cell *D*. By means of the rider *c* the fraction of current passing through the reverser can be modified to any extent. The key *k* being open, the muscle is connected with the shunt and galvanometer, and the direction and extent of the swing noticed. The key *k* is then closed, and by means

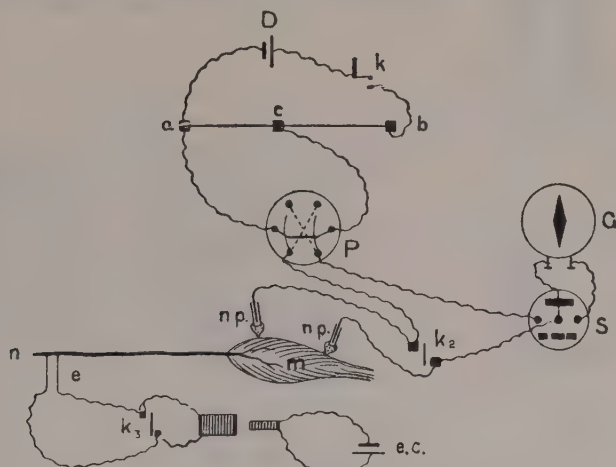


FIG. 90.

of the reverser the current is sent through the galvanometer in the *opposite* direction to the demarcation current, and the rider *c* shifted until the two currents exactly balance one another, and the needle of the galvanometer returns to zero of the scale. If we know

the difference of potential between the two ends of the wire, the proportion $\frac{ac}{ab}$ will give us the E.M.F. of the demarcation current. The galvanometer needle having by compensation been brought to zero, stimulation of the nerve at *e* causes the needle to swing at once in the opposite direction to the first variation. This swing is the measure of the negative variation or current of action.

In order to record the electrical changes accompanying a single muscle twitch, it is necessary to employ some instrument which can react much more rapidly than the ordinary galvanometer. For this purpose we may employ either the capillary electrometer or the string galvanometer of Einthoven or a suitable oscillograph.

The *Capillary Electrometer* is an instrument for recording difference of potential. Its structure is very simple. It consists of a glass tube drawn out to a fine capillary point. This tube with the capillary is filled with mercury. The point dips into a wide tube containing dilute sulphuric acid, at the bottom of which is a little mercury. Two platinum wires fused into the glass and dipping into the mercury serve as terminals. When the instrument is used, the meniscus of the mercury in the capillary at its junction with the acid is observed under the microscope, or a magnified image of it is thrown on a screen with the aid of the electric light. If now the capillary and acid be connected with two points, it will be observed

that any difference in the potential of these two points causes a movement of the meniscus in the direction in which the current is flowing, and the extent of the excursion is proportional to the difference of potential. The excursions lend themselves well to photography, so that we may obtain a graphic record of every electrical variation, and thus determine its extent and its time relations. Somewhat elaborate corrections of the records are necessary however.

It must be remembered that this instrument is an electrometer (measurer of difference of potential), and not a galvanometer (current measurer) so that no current passes the surface. Hence the use of non-polarisable electrodes is not so essential in experiments with this instrument as when we make use of the galvanometer.

In the moving-coil galvanometer the current is sent through a coil of fine wire hung between the poles of a powerful magnet. The same principle in simpler form is made use of in the *String Galvanometer of Einthoven* (Fig. 92). In this a very delicate thread (A A), of silvered quartz or of platinum is stretched between the

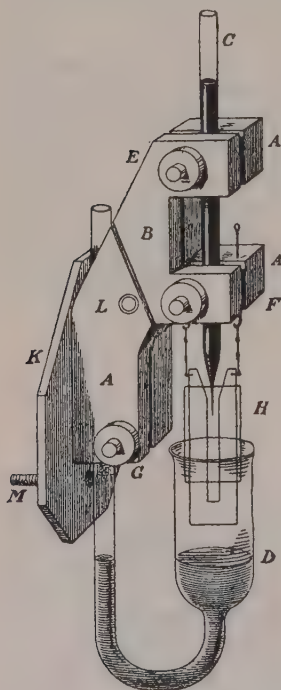


FIG. 91. Capillary Electrometer. (BURCH.)

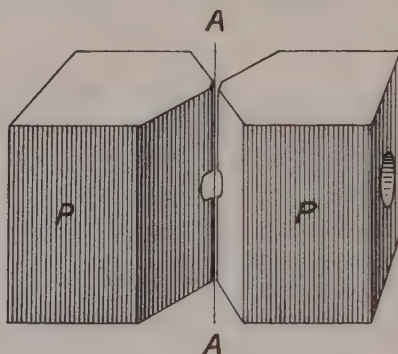


FIG. 92.

poles of a strong magnet. The poles of the magnet are pierced by holes so that the thread may be illuminated by an electric light from one side, and from the other a magnified image of the thread may be thrown upon a screen. Whenever a current passes through the thread it moves laterally, and the lateral movement may be photographed on a moving photographic plate. Owing to the minute dimensions of the thread the instrument is one of extreme delicacy. It will detect very minute

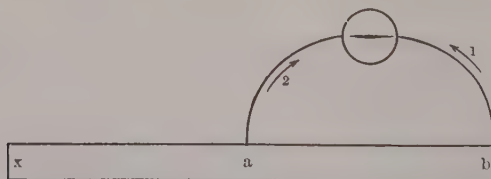


FIG. 93. Diagram showing Diphasic Variation of uninjured Muscle.

currents and will respond reasonably accurately to very rapid changes in potential. The records of rapid fluctuations are more nearly correct than those obtained by the capillary electrometer, but such errors as are present are less amenable to correction.

For very accurate work neither instrument is entirely satisfactory, and it is better to employ a rapidly moving *oscillograph*, such as the one devised by Matthews. This resembles a loud speaker, the plate being replaced by an iron tongue to which a small mirror is attached. The current to be recorded is amplified appropriately by means of

valves. A beam of light is reflected from the mirror, the movements of which can be photographically recorded (Fig. 94).

If a perfectly uninjured regular muscle (Fig. 93) such as the sartorius be kept in moist air and stimulated with a single induction shock at one end, x , and two points, a and b , be led off to a suitable instrument, *e.g.* a string galvanometer, each stimulus applied at x gives rise to a *diphasic* electrical variation. Our study of the mechanical events in muscle has shown that, when the muscle is stimulated at x , a contraction wave commences which travels down the muscle through a and b . The electrical investigation of the muscle shows that excitation of x arouses an electrical change which

also passes down the muscle at the same rate as the mechanical change, which it slightly precedes. If we are leading off from x and a , the electrical change ensues immediately upon stimulus, *i.e.* it has no latent period. On leading off from a and b there is a latent period between the stimulus and the first change, representing the time taken for the change to travel from x to a . When the change reaches a , this becomes the seat of an electromotive force of such a

direction that the current would pass in the outer circuit from b to a (Fig. 93). We may say therefore that a is negative to b . A fraction of a second later the excitatory change has passed on to b and has died away at a . Now b is negative to a , and the current therefore passes in the opposite direction (Fig. 93). Between a and b therefore there is a *diphasic* current, the first phase representing negativity of a to b , and the second phase negativity of b to a . A *diphasic* change is thus also a sign of a propagated change. Every excitation of a normal muscle gives rise to a *diphasic* variation of such a direction that the point stimulated first becomes negative to all other points of the muscle, and this 'negativity,' to use a loose but convenient expression, passes as a wave down the muscle, preceding the wave of contraction and travelling at the same rate.

If one leading-off point be injured, *e.g.* at b , that point becomes permanently negative (injury current), and the change accompanying excitation is absent at that point. A single stimulus applied at x will in this case give only a *monophasic* variation in which a is relatively negative to b (negative variation of demarcation current).

When we study the time relation of the electrical variation ensuing on a single stimulus, we find that the electrical change under the electrodes begins at the moment that the stimulus is applied. It takes about 0.0025 seconds to attain its culminating point. At this point the mechanical change or contraction of the muscle begins. These time relations vary with the temperature of the muscle. We have already seen that the effect of lowering the temperature is to increase that latent period of the contraction. In the same way it slows the rise of the electrical change and the rate of propagation of the wave of electrical change. This is shown in Fig. 95. We are therefore justified in regarding the electrical change as an index to the ionic

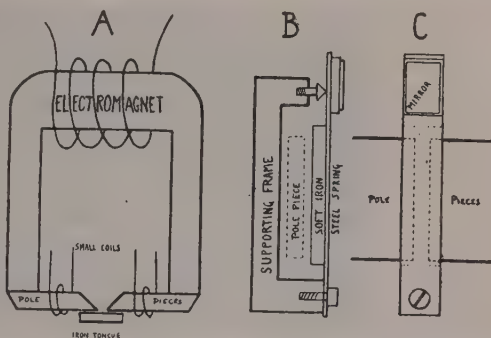


FIG. 94. Diagram of Matthews' Oscillograph. B and C show section and front view of tongue and mirror. (MATTHEWS.)

changes evoked in the muscle as the direct result of the stimulus. The material change in form of each contracting unit is secondary to these changes. As the result of stimulation, a chemical change is aroused at the point of excitation, and travels thence along the muscle fibre at a rate of about 3 metres per second, *i.e.* the same rate as that of the following wave of mechanical change and, like this, varying with the temperature.

Under no conditions, however, may an excitatory condition be propagated without the presence of a contraction, though often this may be so small as to be difficult of detection. When a muscle is so treated as to diminish its mechanical response, *e.g.* by

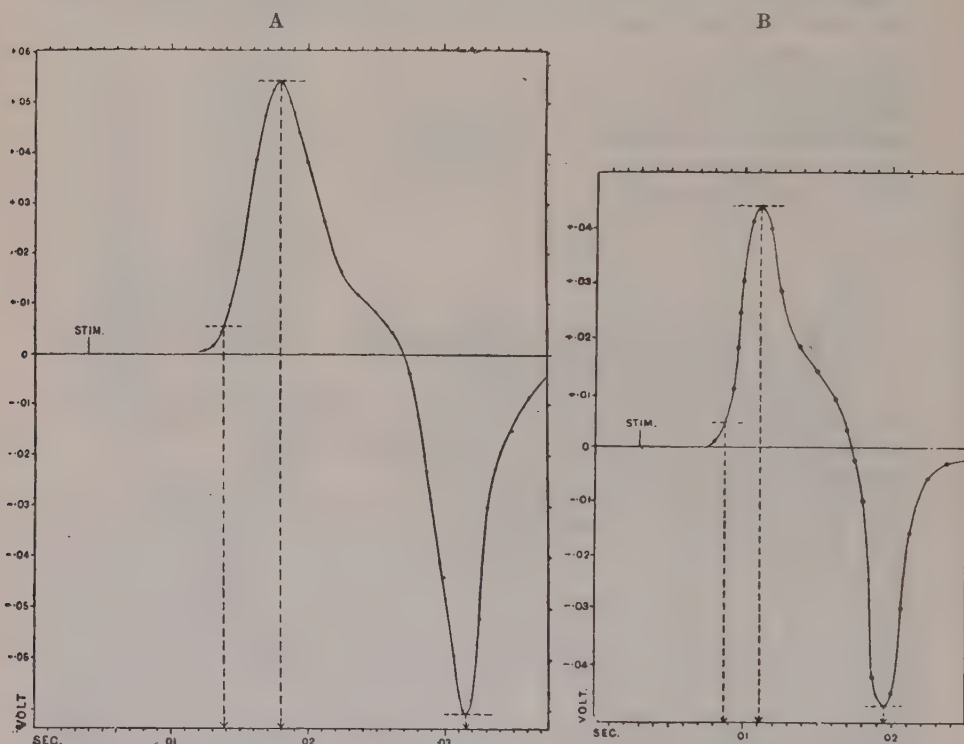


FIG. 95. Diphasic Response of uninjured Sartorius (obtained by analysis of capillary electrometer curves) A, at 8° C.; B, at 18° C. (KEITH LUCAS.)

soaking in water, the electrical response is also reduced, and the two finally vanish together when the muscle passes into "water rigor."

The connection of a diphasic current of action with an excited condition of the tissues passing as a wave from one end to the other is shown still more clearly on a slowly contracting tissue, such as the ventricle of the frog or tortoise. Fig. 96, A, is a photographic record of the variation obtained from the tortoise ventricle, which is led off to a capillary electrometer, one (acid) terminal being connected with the base of the ventricle, the other (mercury) with the apex. Each part of the ventricle remains contracted for a period of $1\frac{1}{2}$ to 2 seconds, and then the contraction passes off, first at the base and later at the apex. The electrical events are an exact replica of the mechanical. Directly after the stimulus has been applied, the base becomes negative and the column of mercury moves up. A moment later the excitatory condition extends to the apex. There is thus a sudden equalisation of potential

between the two terminals, and the mercury comes back quickly to the base line. Here it stays for $1\frac{1}{2}$ to 2 seconds. During this time the whole heart is in an excited condition. Both base and apex are equally excited, and there can be no difference of potential between them. The excitatory condition then passes off, first at the base and then at the apex. There is thus a small period of time in which the apex is still contracted or excited while the base is relaxed, and the apex is therefore negative to the base. This terminal negativity of the apex is shown on the photograph by the excursion of the column of mercury away from the point of the capillary. If one terminal, *e.g.* the apex, be injured, we obtain quite a different variation which is shown

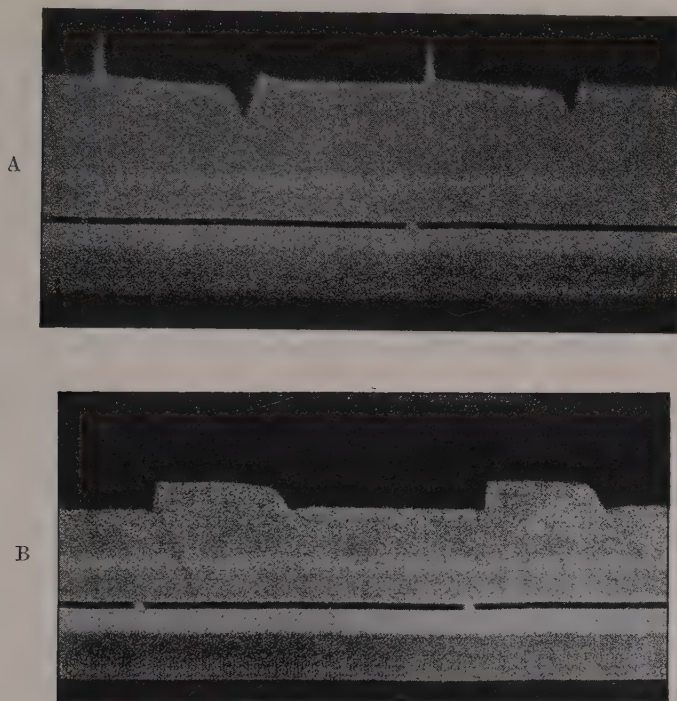


FIG. 96. Electrometer Records of the Electrical Variations in a Tortoise Ventricle, excited to beat rhythmically by single shocks.

A, Ventricle uninjured. B, One leading off spot injured. (BURDON-SANDERSON.)

in Fig. 96, B. It is evident from this figure that in the heart muscle the electrical sign lasts practically as long as the mechanical sign of the excited state.

The only difference between the electrical changes in this case and in that of voluntary muscle is that in the latter all processes are very much quicker, so that as a rule the point *a* (Fig. 93) has ceased to be negative before the negativity of *b* has attained its full height, and there is thus no prolonged equipotential stage.

The electrical variation obtained by leading off a heart beating normally is a much more complex affair, owing to the fact that, for physical reasons, the simple diphasic waves obtained from strips of tissue suspended in air are complicated when the tissues are immersed in fluids (Craib). The question will be discussed more fully in Chapter XXXIII.

THE INTIMATE NATURE OF MUSCULAR CONTRACTION

Experiments on the metabolism of the body as a whole show that the energy of muscular work is derived from the oxidation of the foodstuffs. In man the performance of work involves an increase of the oxidative processes of the body with a corresponding evolution of energy, of which four-fifths will appear as heat while one-fifth may be transformed into mechanical work. In this respect the physiological mechanisms for the production of mechanical energy resemble the greater number of the machines employed by man for the same purpose. In the steam engine and internal combustion engine the whole energy set free by the process of oxidation appears *first* as heat, and then a certain portion of the heat is converted into mechanical work. There is a limit to the efficiency of such heat engines, depending on the maximum differences of temperature available between the two sides of the working part of the machine. The

efficiency of any heat engine is expressed by the formula $E = \frac{T - T^1}{T}$, where T is the highest temperature (in absolute measurement) obtained by the working substance and T^1 is the lowest temperature of the same substance. Ordinary engines rarely attain even half this ideal efficiency, but the greater the difference of temperature available the greater will be the efficiency of the machine. Internal combustion engines, such as the gas or petrol engine, therefore give a greater percentage of the total energy of the fuel out as mechanical energy than is the case with the steam engine.

Engelmann imagined that the chemical changes in the muscle liberate heat and that the effect of this heat upon the doubly refractive particles is to make them imbibe the surrounding water so that they alter from an oval to a spherical shape. It would be impossible however for such large changes of temperature as would be required to take place in the muscle without destroying it, so that we cannot regard muscle as a heat-engine of any type.

Under certain conditions we may obtain by a machine almost the entire energy of a chemical change. We may use for instance a series of cells to drive an electric motor and allow the motor to perform mechanical work. Under these circumstances we could theoretically obtain 100 per cent. of the total chemical energy available, and in conditions of practice the efficiency of the machine may attain to 70 or 80 per cent. A similar arrangement might be present in the ultimate contracting elements of the muscle fibre. The mechanism in the fibre must be one which will provide for a more or less direct transformation of chemical energy into mechanical energy without a previous conversion of the chemical into heat energy. In the living body, where everything is in solution, all the energies may be reduced to one of two kinds, osmotic energy and surface energy. The contractile machine must therefore be one which employs one or other, or both, of these forms of energy. We might, with Macdougall, regard the contractile element as a cylindrical structure differing in its contents from the surrounding sarcoplasm. When the muscle is at rest the contents of the muscle prism will be in equilibrium with the surrounding sarcoplasm. We might imagine the excitatory process to consist in a sudden chemical change occurring in the contents of the muscle prism. The production of a number of new molecules (*e.g.* of lactic acid) would raise the osmotic pressure within the prism and occasion a rapid flow of water from the sarcoplasm. As a result the pressure in the muscle prism would rise and cause a bulging of its lateral wall and a shortening of the whole element. The subsequent phase of relaxation may be due either to a secondary change, *e.g.* neutralisation, leading to the formation of a substance to which the walls of the prism are freely permeable, or to the gradual leak of the primary products of oxidation or disintegration into the sarcoplasm. The substance or substances, giving rise to the osmotic differences which determine contraction, may be either products such as lactic acid, which are formed during contraction, or may possibly be of the nature of neutral salts set free from some condition of combination with the proteins of the sarcolemmal element. Macdonald has brought forward micro-chemical evidence of the appearance of potassium salts in the sarcolemmal element during the state of activity of the muscle.

On the other hand, Bernstein has suggested that the changes during muscular contraction are determined by alterations in surface tension. If a little mercury be spilt on a plate the particles form globules. They are kept from spreading themselves out in thin film under the influence of gravity in consequence of the surface tension of the mercury. Any modification of the surface will alter the tension and therefore state of expansion of the globule. Thus if the globule be in sulphuric acid, it undergoes a certain amount of polarisation and becomes positively charged. By altering the charge of such

a globule we can change its shape as shown diagrammatically in Fig. 97. If *b* represents the shape of the globule lying on the plate in some weak sulphuric acid, *a* will represent the shape of the globule when it is connected with the negative pole of a battery, while *c* will represent its shape when it is connected with the positive pole of a battery, the other pole in each case being connected with the acid. If we consider muscle as made up of a series of chains of oval particles, a chemical change in the surface of these particles, causing an increase of surface tension, will tend to make them assume the globular shape, and will therefore cause a shortening and thickening of the whole fibre.

According to Schafer, contraction is associated with a flow of the outer hyaline contents of the sarcous element into the tubular structure forming the middle portion. Such a flow may be determined either by osmotic differences between the centre and periphery of the sarcous element, or by a change in the surface tension obtaining between the isotropic fluid at the ends and the anisotropic structures in the centre of the muscle prism.

In favour of the hypothesis that the essential factor in the processes of excitation and contraction is an alteration of surface, we may note that the electrical changes accompanying the excitatory process denote a polarisation or accumulation of ions on the surfaces situated in the excited area. The chemical change which is responsible for the current of action at the excited spot takes place almost instantaneously and disappears somewhat more slowly. It would seem that the excitatory process consists essentially in the setting free of certain ions on the surface or surfaces in the contractile tissue, and that the passing away of the excitatory state is due to the disappearance of these ions, either by diffusion away into the surrounding fluid or by further chemical changes such as oxidation. A study of the development

of tension and of heat production in a muscle on excitation has shown that in both cases the yield of energy on excitation is within limits increased by lengthening and diminished by shortening the muscle. Now alteration in length of the muscle will not alter its volume but will alter the extent of

its longitudinal surfaces, and it appears therefore that the production of heat as well as of mechanical energy is not a volume but a surface effect. Finally the work of A. V. Hill on the heat production in muscle indicates that the rise of tension in a muscle on excitation is due to the liberation of chemical bodies, of which lactic acid is probably one, in the neighbourhood of certain longitudinal surfaces or membranes, and that the presence of these bodies changes the tension at such surfaces and thereby the longitudinal tension of the fibre. The extent and intensity of the production of these bodies must depend on the area of the chemically active surfaces and therefore on the length of the muscle fibres. The muscle reacts at the end of the excitatory stage, not by any active process of lengthening, but by neutralisation, or simple physical diffusion of the active chemical bodies away from the interfaces or membranes. Later on lactic acid is removed under the influence of oxygen with the production of carbon dioxide and a further amount of heat.

Although the oxidative processes are responsible ultimately for all the energies of the higher animal, no oxidative change is involved in the production of lactic acid, nor is the presence of oxygen necessary for the contraction of muscle to take place. On the other hand, if we wish to obtain the maximum amount of work from a muscle, we must supply it richly with oxygen, the presence of which is essential to the stage of recovery. It is as if the process of oxidation furnished the energy for winding up a spring, whereas excitation removed a catch and allowed the spring to run down, setting free this energy for the performance of work or for conversion into heat.

A. V. Hill has recently pointed out that the number of molecules of lactic acid coming into existence at the moment of excitation is not sufficient to account for a rise of surface tension which would give the contractile stress actually set up in the muscle. The exact mechanism by which the chemical energy of the contracting muscle is converted into the mechanical energy of shortening and increased tension is thus still unelucidated.

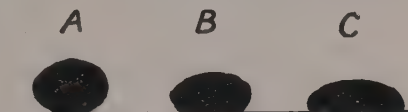


FIG. 97.

CHAPTER XII

PLAIN MUSCLE AND OTHER CONTRACTILE TISSUES

OUR knowledge of the physiology of unstriated (also called smooth, plain, or involuntary) muscle is derived from experiments on viscera or organs in which it predominates, *e.g.* the uterus, arteries, stomach, the intestine, ureter, bladder and retractor penis.* This tissue differs from voluntary muscle in containing numerous plexuses of nerve fibres (non-medullated) and ganglion cells, so that in all our researches it is difficult to be certain whether the results are due to the muscle fibres themselves, or to the nerves and nerve cells which are so intimately connected with them; especially as we have as yet no convenient drug like curare by aid of which we might discriminate between action on muscle and action on nerve.

A further difficulty is that the physiological properties of plain muscle differ with its source, so that it is unsafe to generalise from the results of specific experiments with tissue from only one source. At the one extreme, smooth muscle preserves many of the properties of primitive protoplasm, while at the other it presents properties which indicate a differentiation of function at least as striking as in striated muscle. In general, however, it is distinguished from voluntary muscle not only by its histological structure, in its chemistry, its innervation, and its physical properties, but especially by the phenomena of independent tonus and rhythmic contraction.

The individual fibres of plain muscle are fusiform cells (Fig. 539), with a centrally placed nucleus; the cytoplasm in the living cell appears to be structureless, and there is a delicate cell wall. The cells are probably connected together by fine intercellular bridges to form a syncytium, by which in all probability the excitatory process can be transmitted from cell to cell, though under conditions which are at present unknown.

The most striking differences in chemical composition between striated and plain muscle are that the latter contains much less soluble protein, only very small quantities of creatine (and phosphagen), smaller amounts of glycogen, less potassium and phosphate and more sodium than the former.

INNERVATION. Skeletal muscle is entirely dependent for its activity on the central nervous system, through the intermediation of the motor nerves. When the nerves to such a muscle are cut it is flabby and motionless and soon atrophies.

In the case of smooth muscle, there is a double nerve supply, one variety being motor, and resembling the motor supply of skeletal muscle, the other kind inhibitory, and causing cessation of a previous contraction. All these fibres belong to the autonomic system, *i.e.* they arise from ganglion cells outside the central nervous system, and only receive impulses from the central nervous system through the intermediation of these ganglia. Usually one supply is sympathetic, and the other parasympathetic, *e.g.* to the intestinal muscle, sympathetic and vagus: their ultimate ramifications in the muscle form a plexus, and are non-medullated, and not infrequently the ganglion cells from which they arise are also contained in the nerve net near to or among the plain muscle

* The *retractor penis*, found in the dog, cat, horse, hedgehog (but not in rabbit or man), is a thin band of longitudinally arranged unstriated muscle, which is inserted at the attachment of the prepuce and is continued backwards in a sheath of connective tissue to the bulb, where it divides into two slips, which pass on either side of the anus. It is innervated from two sources, the *motor* fibres being derived from the lumbar sympathetic and running to the muscle in the internal pudic nerve, while the *inhibitory* fibres run in the pelvic visceral nerves (*nervi erigentes*) and are derived from the second and third sacral nerve roots.

cells which they supply. It is believed that both sources of supply are present in the nerve plexus, *e.g.* both vagus and sympathetic fibres are present in the plexus of Auerbach in the intestine.

The physiological significance of the double supply is evident from the fact that, even when deprived of all nerves, plain muscle may exhibit either sustained spontaneous contractions, known as tonic, or else intermittent rhythmic contractions, so that control



FIG. 98. Tracing from the *Retractor Penis* Muscle of the Dog, showing lengthening (inhibition) on stimulation of the *nervus erigens*, and a smart contraction on stimulating the *pudic* (motor) nerve. (Movements of muscle reduced $\frac{1}{2}$.)

of both contraction and relaxation is essential (Fig. 98). In some invertebrates many voluntary striated muscles also possess a double nerve supply, one causing contraction of the relaxed muscle, and one causing relaxation of the contracted muscle (Fig. 99).

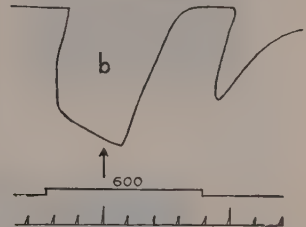


FIG. 99. Tracing of Contraction of Adductor Muscle of Claw of Crayfish, showing inhibition resulting from stimulation of its nerve (at *b*) by means of a constant current. The break of the current causes a second smaller inhibition. (BIEDERMANN.)

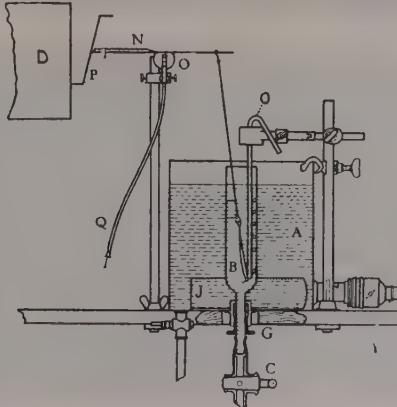


FIG. 100. Thermostat Bath for Investigation of Plain Muscle. A = copper water-bath, kept warm by the lamp J. B = Glass vessel filled with warm saline which can be changed by the tap C. O = the oxygen tube, at the bottom of which is a platinum pin with which the tissue is transfixed. N = a frontal writing lever, to which the tissue is attached by a hair. O, Q = a small brake for fixing the lever while the fluid is changed in B. D = recording drum. (BURN and DALE.)

PHYSIOLOGICAL PROPERTIES. In studying the responses of plain muscle it is not customary, as with skeletal muscle, to use the moist tissue suspended in air, because under these conditions the tissue behaves irregularly, but, instead, to suspend it in a bath of saline solution of suitable composition, *e.g.* Ringer's fluid, which is kept at the proper temperature and oxygenated with a constant stream of oxygen bubbles. A suitable arrangement is shown in Fig. 100.

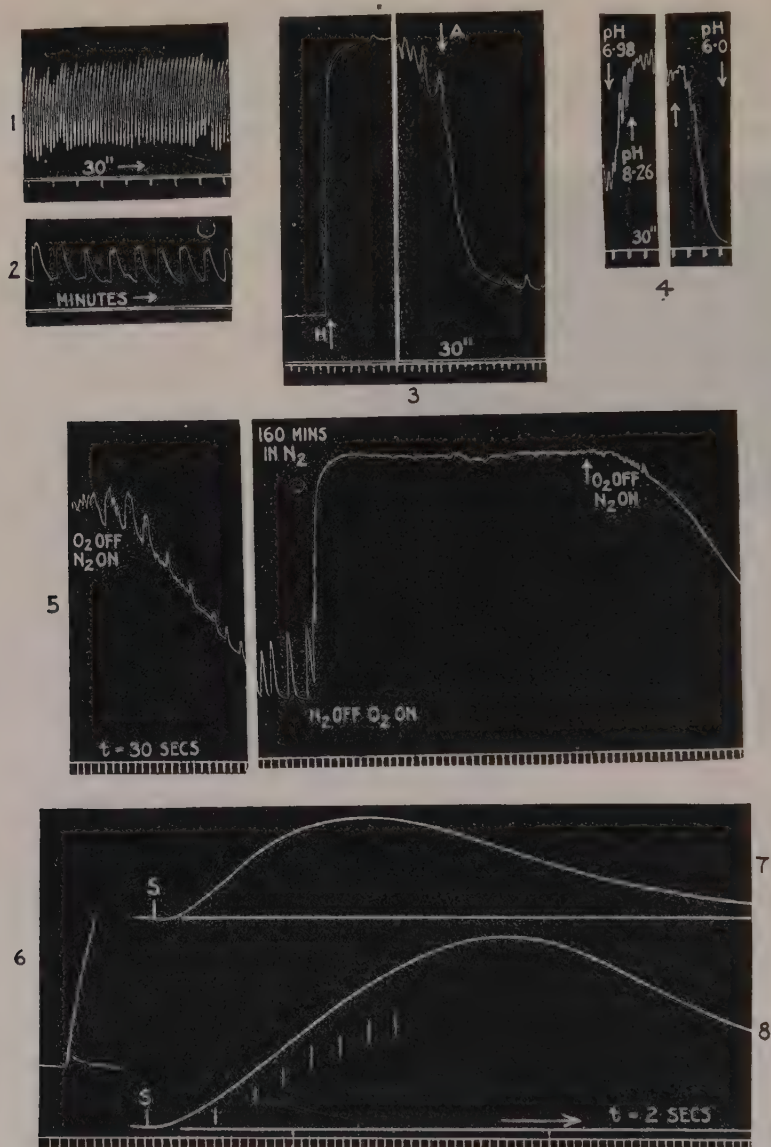


FIG. 101. 1. Isolated jejunum of rabbit, showing rhythmic contractions. Time tracing = 30 seconds.
 2. Slow rhythmic contractions of guinea-pig uterus. (Time, same scale as 1.)
 3. Guinea-pig uterus. At H, histamine 1 in 1 million; at A, adrenaline, 1 in 4 million. Time = 30 seconds.
 4. Small intestine of cat, showing contraction on raising, and relaxation on lowering the pH of the fluid in the bath. Time = 30 seconds; pH measurements taken at arrow. (EVANS and UNDERHILL.)
 5. Uterus of cat, showing effect of oxygen lack caused by replacing oxygen bubbles by nitrogen. The second portion is taken after about two and a half hours in nitrogen.
 6. On left, contraction of frog's gastrocnemius to compare with contraction of frog's stomach (7) on same slow drum. Point of stimulation = S. 8. Summation of contraction in frog's stomach. The first stimulus is followed by seven others at the points shown.

Tonus. Plain muscle, isolated in this manner, is very readily extensible, so that when a small weight is applied to it the tissue may extend to several times its former length; the effect of the weight will depend, however, on the degree of *tonus* which the preparation has, and this varies with the source. Thus the cat's uterus is highly tonic and requires a much larger weight to stretch it than does a guinea-pig's uterus of the same size. Many drugs have the property of affecting the tonus of plain muscle, perhaps by exciting the sympathetic or parasympathetic nerve structures contained within it. Thus adrenaline will cause the uterus to relax (if tonic), while acetyl choline even in high dilutions (e.g. 1 part in 10 million of saline) or histamine causes intense tonic contraction (Fig. 101, 3). Adrenaline in many other respects reproduces the action of the sympathetic nerves, and is therefore called *sympathicomimetic*, while acetyl choline reproduces the action of the parasympathetic nerve supply.

The maintenance of the sustained contraction known as tonus is apparently not associated with increased expenditure of energy, for the tissue, while in this condition, uses no more oxygen than when in the relaxed state, even though it may be exerting quite considerable tension; consequently no signs of fatigue are manifested. Thus in the bivalve mollusc *Pecten*, there is a large striated adductor muscle which can close the shell rapidly but then relaxes, and a smaller smooth muscle whose office it is to hold the two valves together. The weight required to separate the valves, when this latter muscle is contracted, is many times that which will prevent the closure of the shell when open. Thus the smooth adductor muscle can support a weight which it cannot raise. This "catch action" is under the control of the central nervous system by two nerves from the cerebral ganglion. Stimulation of one of these causes contraction, and the muscle remains contracted even after the nerve is divided. Stimulation of the other nerve causes the muscle to relax, so that the shell opens. Apparently the action of these nerves is to allow the length of the muscle to alter, and it then remains at that length until the other nerve is stimulated. Somewhat similar phenomena may be observed in the smooth muscle of higher animals, and it may be that most smooth muscles are capable of two kinds of shortening, one followed by passive relaxation and the other by fixation at a diminished length without the expenditure of extra energy.

Although plain muscle can execute contractions for some time after being completely deprived of oxygen, and although, when in the tonic state, the muscle uses no more oxygen than when it is relaxed, yet the presence of oxygen is essential for the maintenance of tonus (Fig. 101, 5). It would seem as though oxygen, though not essential for the act of shortening, plays some part in maintaining the integrity of the cell structures which are concerned in fixing the tissue at the shorter length. (GARRY.)

Rhythmic Contractions. Most varieties of plain muscle when slightly stretched normally exhibit rhythmic contractions at fairly regular intervals, both in the body and when isolated. The strength and frequency of these rhythmic contractions vary very much according to conditions; in some types of plain muscle, e.g. that of the small intestine, they are quite regular, frequent and powerful (Fig. 101, 1), whereas in other cases they are slow (Fig. 101, 2), often irregular, and of variable amplitude, being occasionally negligible.

There is strong evidence that they originate in the plain muscle cells themselves, i.e. they are myogenic; for example, the cells in the chick amnion, which are devoid of nerves, show these rhythmic contractions; further, strips of the inner muscular coat of the small intestine, also free from nerve structures, were found by Gunn and Underhill to exhibit rhythmic contractions.

Stimulation. Smooth muscle responds to very various stimuli, electrical, mechanical, thermal, light, chemical, etc. As we should expect however from the sluggish response of this kind of contractile tissue (high chronaxie), the optimum rate of change of current which excites is very much slower than in the case of striated muscle. Thus in many instances a single induction shock, even if very strong, is powerless to excite contraction, and the make-induction shock of long duration and low intensity is always more efficacious than the short sharp break-induction current. A still better stimulus is the make or break of a constant current. When the latter form of stimulation is used, response occurs at the make sooner than at the break and, just as in other tissues, the make excitation starts from the cathode and the break excitation from the anode.

The contraction curve of plain muscle, though very variable, is much slower than that of voluntary muscle, and the phenomena of latent period, shortening, and relaxation can easily be followed with the eye. The latent period may be from 0.2 to one or two seconds, and the period of contraction from half a second to a few minutes, with proportional durations of relaxation (Fig. 101, 7); the stronger the stimulus the shorter the latent period and the higher the contraction. As with other forms of muscle, the strength of a contraction also increases, within limits, with increased initial length of the fibres, a very important property in view of the common occurrence of plain muscle in the walls of hollow viscera, where it is subjected to various degrees of extension.

In voluntary muscle, if one stimulus follows another at a sufficiently short interval, so that two stimuli fall within the period of rise of contractile stress, an increased height of contraction is obtained under all conditions. If the interval between two stimuli be so short that the second falls within what we have called the refractory period due to the first stimulus, no summation is obtained, the second stimulus being ineffective.

In the slow contraction of involuntary muscle we also have an increased liberation of energy due to repetition of the stimulus during the rise of the excitatory condition (Fig. 101, 8). As might be expected the refractory period is also longer in involuntary muscle.

In all involuntary muscle we may observe summation of the effects of stimuli even when each individual stimulus is insufficient to produce any excitation. Thus in a muscle such as the retractor penis, we may find a strength of induction shock which, applied singly, is just insufficient to evoke any response. If however the shocks are repeated at intervals of a second, it will be found that the first three or four stimuli are ineffective, and then the muscle enters into a contraction which increases with each succeeding stimulus until it has attained its maximum. There is thus summation *before* any contraction has occurred, a *summation of stimuli*. Each stimulus in fact alters the state of the contractile tissue and makes it more ready to respond to the next stimulus, so that the stimuli become more and more effective.

We shall meet with other examples of this summation of stimuli when dealing with the physiology of the central nervous system. It is indeed a fundamental phenomenon in the physiology of excitation.

CHEMICAL STIMULATION. Strong salt solution excites contractions just as in the case of skeletal muscle. The tissue is also very sensitive to alterations in the hydrogen ion concentration; within limits, lowering of H-ion causes contraction or tonus, with increased rate of rhythmic contractions, while increase causes the reverse (Fig. 101, 4). Many drugs, such as physostigmine, salts of lead and barium, histamine, acetyl choline, pilocarpine, may act directly on smooth muscle and cause contraction. As one would expect however from the greater independence of the smooth muscle,

the action of these drugs varies from organ to organ, muscle fibres apparently histologically identical reacting diversely according to their origin. Some of these drugs, *e.g.* barium salts and perhaps pituitrin, appear to act directly on the muscle cells, while others, *e.g.* nicotine, exert their action on the accompanying nerves; the latter is true also of adrenaline which, accordingly, may cause either relaxation (*e.g.* of intestine) or contraction (*e.g.* of retractor penis).

MECHANICAL STIMULATION. Smooth muscle is very sensitive to mechanical stimuli, and may react to a local pinch or blow with a local or a general (propagated) contraction. The most important form of mechanical stimulation is that produced by tension. The effect of increasing the tension on smooth muscle may be twofold: causing in the first place extension and in the second excitation with increased contraction. These two effects may be illustrated by taking the case of the bladder. If this viscus (which is surrounded by a complete coat of smooth muscle) has all its connections with the central nervous system severed, it is when empty in a state of tonic contraction. If fluid be injected into it rapidly, there is a great rise of pressure in its cavity due to the forcible distension. If however the fluid be injected slowly, the bladder muscle relaxes to make room for it, so that a considerable amount of fluid may be accommodated in the bladder without any great rise of pressure. This process of relaxation has its limit. If the injection of fluid be continued, the walls begin to be stretched passively, and this increased tension acts as a stimulus causing rhythmic contractions of the whole bladder.

A peculiar property of plain muscle is that a stimulus (*e.g.* electrical or mechanical) which, when applied to the relaxed muscle causes a contraction, will, when applied to the tonically contracted muscle, often provoke a rapid relaxation, and *vice versa*. This property is perhaps responsible for the occurrence of rhythmic contractions when the muscle is given the constant stimulus of a slight stretch; this alternately excites the extended muscle to contract and the contracted muscle to relax.

PROPAGATION OF THE EXCITATORY STATE, OR WAVE OF CONTRACTION. On stimulating any part of a voluntary muscle fibre, a wave of contraction is started which travels to each end of the fibre, but no further. There is no propagation from muscle fibre to muscle fibre, the synchronous contraction of the whole muscle being brought about when there is simultaneous excitation of all its fibres. This isolation of the excitatory state is not found in smooth muscle. Frequently a stimulus applied to any part of a sheet of smooth fibres may travel all over the sheet just as if it were a single fibre. It seems probable indeed that there is protoplasmic continuity by means of fine bridge-like processes between adjacent muscle cells; and even in the absence of such bridges the propagation of the contraction could perhaps be accounted for by excitation of each fibre by the action current of its neighbours.

We do not know whether each fibre of smooth muscle gives an all-or-none response to a stimulus, nor do we know what is the duration of the contraction of each fibre relative to that of a whole mass of tissue; consequently we are not in a position to say whether the contraction curve as commonly recorded represents the simultaneous or the successive action of the component cells, or whether a feeble contraction is due to the smaller effort of all the cells, or to an all or none response of only a few of them. The analogy with other tissues, as well as some direct evidence, however, suggests the latter: it is certain for instance that feeble stimuli may produce only local contraction, especially in fatigued tissue. Thus, in the retractor penis of the dog, we get graded contractions from graded stimuli, and it is noticeable that with increasing strength of stimulus a greater extent of muscle enters into contraction.

It must be remembered that in all unstriated muscle the fibres are surrounded

by a network of non-medullated nerve fibres. Some physiologists are inclined to ascribe to these fibres an important part in the propagation of the contraction wave.

INFLUENCE OF TEMPERATURE. Smooth muscle is extremely susceptible to changes of temperature; as a rule warming causes relaxation while application of cold causes a tonic contraction. The condition of the muscle at any given time depends not only on its actual temperature but also on the rapidity with which this temperature has been reached. Thus a rapid cooling of the retractor penis muscle of a dog from 35° to 25° may cause a contraction as extensive as would be produced by a slow cooling to 5° C. On warming a muscle from 30° to 50° C. it lengthens gradually up to about 40°, and it may then undergo a marked heat contraction (varying in degree in different muscles) at about 50° C., which may pass off at a somewhat higher temperature. It is first paralysed and then killed somewhere between 40° and 50° C. It seems very doubtful whether any true rigor mortis occurs in smooth muscle. The hard contracted appearance of the smooth muscle in a recently dead animal is chiefly conditioned by the fall of temperature. On excising the muscle and warming it up to body temperature it may again relax and show signs of irritability two or three days after the death of the animal.

The Chemistry of Contraction in plain muscle, so far as it has been studied, is very similar to that in striated muscle. Glycogen disappears and lactic acid arises when the muscle contracts, or when it is asphyxiated or treated with arsenates. The action of caffeine is, however, different, for this retards lactic acid formation in plain muscle. During recovery from contraction lactic acid is removed and glycogen restored. The amounts of lactic acid produced and of glycogen removed in contraction are relatively small.

CARDIAC MUSCLE. The properties of cardiac, or heart muscle will be considered in Chapter XXXIV.

AMŒBOID MOVEMENT

Amœboid movement is seen in the unicellular organisms such as the amœba and in the white blood corpuscles. It can occur only within certain limits of temperature (about 0° to 40° C.); within these limits it is the more active the higher the temperature. At about 45° the cell goes into a condition resembling heat rigor.

The fluid in which the corpuscles are suspended is of great importance. Distilled water, almost all salts, acids and alkalies, if strong enough, stop the action and kill the cell.

The movements are also arrested by CO₂ or by absence of oxygen.

Artificial excitation, whether electrical, chemical or thermal, causes universal contraction of the corpuscle which therefore assumes the spherical form.

CILIARY MOVEMENT

Cilia are met with in man in nearly the whole of the respiratory passages and the cavities opening into them, in the generative organs, in the uterus and Fallopian tubes of the female and the epididymis of the male, and on the ependyma of the central canal of the spinal cord and its continuation into the cerebral ventricles.

The cilia (Fig. 102) are delicate tapering filaments which project from the hyaline border of the epithelial cells. There are about twenty or

thirty to each cell. The hyaline border is really made up of the enlarged basal portions of the cilia.

In action the cilia bend suddenly down into a hook or sickle form, and then return slowly to the erect position. This movement is repeated many (twelve to twenty) times a second, and thus serves to move forward mucus, dust or an ovum, as the case may be. The movement seems to be entirely automatic, and it is quite unaffected by nerves, at any rate in all the higher animals.

The trachea of a mammal slit open along the back and pinned out under warm oxygenated Ringer's solution forms a suitable object for demonstrating ciliary action. If a drop of graphite suspension be placed on the mucous membrane, it will be seen to become entangled in mucus and pushed towards the upper end of the trachea at the rate of 1 to 2 cm. per minute. By this means any dust particles trapped on the ciliated surfaces of the respiratory tract are swept upwards to the mouth.

There seems to be a functional connection between all the cells of a ciliated epithelial surface. Movement of the cilia in each cell is synchronous, and the action is passed from cell to cell in succession, just as, when the wind blows, waves of bending pass over a field of corn.

The condition of ciliary action are the same as those for amœboid movement of naked cells. Acids or excess of calcium ions slow, and alkalies or potassium ions hasten the rate of action. Rise of temperature, within limits hastens, and cold slows, the rate, but over most of these ranges the amplitude of the movement is constant. Oxygen is utilised at a rate proportional to the rate of ciliary action, and though ciliary action will persist for a time in its absence, the movement ultimately fails if it is withheld (Gray).

The minuteness of the object has up to now prevented us from deciding whether the cilium is itself actively contractile, or whether it is simply passively moved by the action of the basal part situated in the hyaline border of the cell.

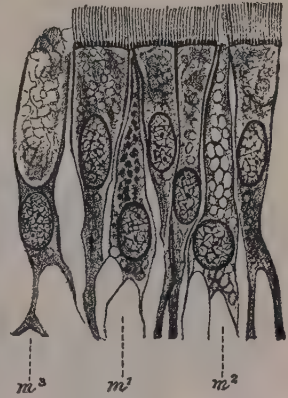


FIG. 102. Ciliated Columnar Epithelium from the Trachea of a Rabbit; m^1 , m^2 , m^3 , mucus-secreting cells. (SCHAFER.)

CHAPTER XIII

NERVE FIBRES

THE STRUCTURE OF NERVE FIBRES

ON stimulating the nerve of a nerve muscle preparation at any part, the stimulus is followed after a very short interval by a contraction of the muscle. This observation illustrates the two functions of nerve fibres, irritability and conductivity—that is to say, a suitable stimulus can set up in any part of the nerve a disturbance which is propagated down the nerve without any visible effects occurring in it; and it is not until this nervous impulse has reached the muscle that a visible effect is observed in the shape of a contraction. In the animal body a direct excitation of the nerve fibre in its course never takes place under normal circumstances. The only function the nerve fibre has to perform is that of conducting impulses from the sense organs at the periphery to the central nervous system, and efferent impulses from this to the muscles and other of its servants. Hence it is absolutely essential that there should be vital continuity along the whole length of the fibre. Damage to any part, such as by crushing, heat or any other injurious condition, infallibly causes a block to the passage of an impulse.

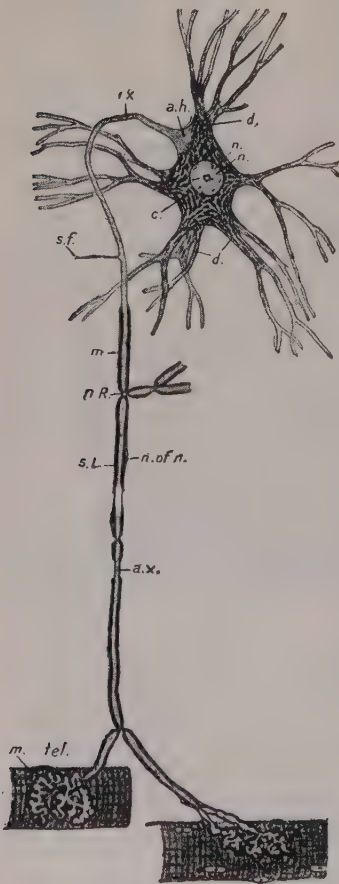


FIG. 103. Diagram of a Motor Nerve Cell with its Nerve Fibre. (After BARKER.)

a.h., axon hillock; *d.*, dendrites; *a.x.*, axis cylinder; *m.*, medullary sheath; *n.R.*, node of Ranvier.

A nerve fibre is essentially a long process or arm of a nerve cell (Fig. 103). The cell may either be situated on the surface of the body or, as in most cases in the higher animals, may be withdrawn from the surface into a special collection of cells such as the posterior root ganglion, or may be one of the mass of cells and interlacing processes making up a central nervous system. All nerves are alike in possessing as their conducting part the continuous strand of protoplasm produced from the nerve cell and known as the *axon* or *axis cylinder*. By special methods the axon may be shown to be made up of *fibrillæ* or *neuro-fibrils*, embedded in a more fluid material (Fig. 104). These neuro-fibrils are supposed to be continuous throughout the cell and the axis cylinder

and to represent the essential conducting constituents of the nerve. In the course of growth the nerves develop certain histological differences, which appear to bear some relation to the nature of the processes they conduct or to the character of their parent cell. Thus all the fibres which are given off from and which enter the central nervous system, *i.e.* the brain and spinal cord, belong to the class known as *medullated*. In this type the conducting core or axis cylinder is surrounded with a layer of material known as *myelin*, forming the *medullary sheath*. This sheath consists of a fatty material composed largely of lecithin, and staining black with osmic acid, supported in the interstices of a network formed of a horny substance known as *neuro-keratin*. The medullary sheath is surrounded by a structureless membrane, the primitive sheath or *neurilemma*. At regular intervals a break occurs in the medullary sheath, the neurilemma coming in close contact with the axis cylinder. This break is the *node of Ranvier*, the intervening portions of medullated nerve being the *internodes*. In each internode, lying closely under the neurilemma, is an oval nucleus embedded in a little granular protoplasm. The medullated nerve fibres vary considerably in diameter, the largest fibres being distributed to the muscles and skin, the smallest carrying impulses from the central nervous system to the viscera. The latter all come to an end in some collection of ganglion cells of the sympathetic chain or peripheral ganglia, the impulses being carried on to their destination by a fresh relay of non-medullated nerve fibres.

The non-medullated fibres (Fig. 105) differ from the medullated simply in the absence of a medullary sheath. They possess a primitive sheath, under which we find nuclei lying closely on the side of the fibre and bulging out the sheath. In their ultimate ramifications they tend to form close networks or plexuses and appear to lose the last traces of a sheath.

The medullated nerves are bound together by connective tissue (*endoneurium*) into small bundles, which are again united by tougher connective tissue into larger nerve trunks. The fibres as a rule branch only when in close proximity to their destination, and then the branching always occurs at a node of Ranvier.

As to the functions of the myelin sheath in the medullated nerve fibre very little

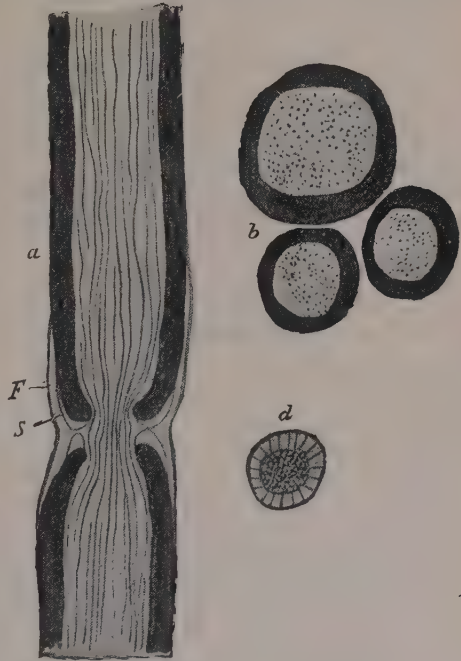


FIG. 104. Medullated Nerve Fibres, showing Continuity of the Neuro-fibrils across the Node of Ranvier. (BETHE.)

a, longitudinal; *b*, transverse section of internode. *d* = transverse section at node.



FIG. 105. Non-medullated Nerve Fibres. (SCHAFFER.)

is known. It does not make its appearance until the axis cylinder is formed, and is apparently derived from a series of cells which grow out from the spongioblasts of the central nervous system and form a chain surrounding the out-growing axons. In the regeneration of a nerve fibre after section, the myelin sheath appears later than the axon in the peripheral part of the nerve. It has been supposed by some to act as a sort of insulator ensuring isolated conduction within any given nerve fibre. We have however no proof that equally isolated conduction is not possible in the non-medullated fibres of the visceral system, although it is certainly true that a finer ordering of move-

ments is required in the skeletal muscles than in the visceral unstriated muscles. Moreover in the central nervous system the main tracts cannot be shown to be functional before the date at which they acquire their medullary sheaths, suggesting that previously any impulse making its way along the tract underwent dissipation before arriving at its destination. It is possible too that the myelin sheath may serve as a source of nutrition to the enclosed axis cylinder which, in the greater part of its course, is far removed from its trophic centre, namely the cell of which it is an outgrowth. This trophic function of the myelin sheath has a certain basis of fact in that the myelin sheath is as a rule larger in those fibres which take the longer course.

PROPAGATION ALONG NERVE FIBRES

The velocity of propagation along a nerve fibre may easily be measured. To measure the velocity of propagation in a motor nerve, a frog's gastrocnemius is prepared, with a long piece of sciatic nerve attached. The muscle is arranged (Fig. 106) so that its contraction may be recorded on a rapidly moving surface, on which are also recorded, by means of electro-magnetic

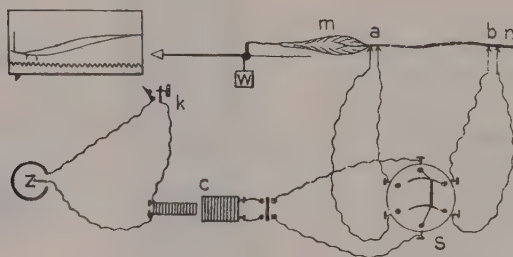


FIG. 106. Diagram of Arrangement of Experiment for the Determination of the Velocity of Transmission of a Motor Impulse down a Nerve.

The battery current passes through the primary coil of the inductorium *c*, and a 'kick over' key *k*. By means of the switch *s*, the break shock in the secondary circuit can be sent through the nerve *n*, either at *b* or at *a*. The muscle *m* is arranged to write on the blackened surface of a trigger or pendulum myograph, and is excited during the passage of the recording surface by the automatic opening of the key *k*. (The time marker is not shown.)

signals, the moment at which the stimulus is sent into the nerve, and also a time tracing. Records are now taken of the contraction of the muscle: first, when the nerve is stimulated at its extreme upper end; secondly, as close as possible to the muscle. It will be found that the latent period, which elapses between the point at which the stimulus is sent into the nerve and the point at which the lever begins to rise, is rather longer in the first case than in the second. The difference in the two latent periods gives the time that the nervous impulse has taken to travel down the length of nerve between the two stimulated points. Calculated in this way, the velocity of propagation in frog's nerve is about 28 metres per second.

In man and in warm-blooded animals the velocity has been estimated at about 120 metres per second.

These values represent the highest average velocities in motor nerves. As a matter of fact, the impulses generated in a nerve of mixed function travel at different speeds, the coarse fibres conducting most quickly. In the frog the speeds in the different fibres of the sciatic nerve range from about 40 metres per second to about 15 metres per second.

On the other hand in invertebrata the velocity of propagation along nerve fibres may be quite slow. The following Table represents the velocity of transmission along a number of different fibres, as determined by Carlson, compared with the duration of a single muscle twitch in the same animal.

Species	Muscle		Nerve	
	Muscle	Contraction time in seconds	Nerve	Rate of the impulse in metres per second
Frog . . .	Gastrocnemius .	0.10	Sciatic (medullated)	27.00
Snake . . .	Hyoglossus .	0.15	Hyoglossal (medullated)	14.004
Lobster . . . (Homarus)	Adductor of forceps	0.25	Ambulacral (non-medullated)	12.00
Hagfish . . .	Retractor of jaw .	0.18	Mandibular (non-medullated)	4.50
Limulus . . .	Adductor of forceps	1.00	Ambulacral (non-medullated)	3.25
Octopus . . .	Mantle .	0.50	Pallial (non-medullated)	2.00
Slug (Limax) .	Foot . . .	4.00	Pedal (non-medullated)	1.25
Limulus . . .	Heart . . .	2.25	Nerve plexus in heart (non-medullated)	0.40

The velocity of propagation in sensory nerves is more difficult to determine owing to the fact that a sensory impulse, on arrival at the receiving organ—*i.e.* some part of the central nervous system—does not at once give rise to some definite recordable mechanical change, such as a muscular contraction. There is another method of determining the velocity of conduction, which may be used also with sensory fibres. The passage of a nerve impulse down a nerve, just as the passage of a wave of contraction along a muscle fibre, is accompanied by an electrical change, which also travels along the nerve as a wave of 'negativity.' The velocity of propagation of this wave may be measured, and is found to give the same ranges as the velocity determined by the preceding method.

The existence of this electrical change enables us to show that a nerve impulse, excited at any point in the course of a nerve fibre, travels *in both directions* along the fibre. The power of nerves to transmit impulses in either direction is shown further by the experiment known as Kühne's gracilis experiment. The gracilis muscle of the frog is separated into two portions by a tendinous intersection, and there is no muscular continuity between the two halves. The nerve to the muscle divides into two branches, one to each half, and at the point of junction *there is division of the axis cylinders themselves*. If the section *a* in the diagram (Fig. 107), which is quite isolated from the rest of the muscle, be stimulated, as by snipping it with scissors, the whole muscle contracts. If the portion of the muscle which is free from nerve fibres be stimulated in the same way, the contraction is limited to the fibres directly stimulated, showing that in the first case the stimulus excited nerve fibres which transmitted the impulse *up* the nerve to the point of division and then *down* again to the other half of the muscle.

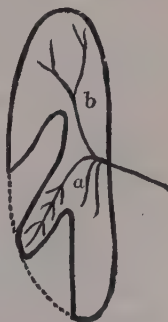


FIG. 107.
Kühne's Gracilis Experiment.

Since nerves have this power of conduction in both directions, it might be thought that a single set of nerve fibres might very well subserve both afferent and efferent functions, at one time conducting sensory impulses from periphery to cord, at another

time motor impulses from cord to muscles. But this is not the case. As a matter of fact we find in the body a marked differentiation of function between various nerve fibres. Thus Bell and Magendie showed that the spinal roots might be divided into efferent and afferent, the anterior roots carrying only impulses from spinal cord to periphery, while the posterior roots carried impulses from periphery to central nervous system. The law known by the name of these observers states indeed that a nerve fibre cannot be both motor and sensory. We may find both kinds of fibres bound up into a single nerve trunk, but the fibres in each case are isolated and conduct impulses only in one or other direction. Under normal conditions the afferent fibres are excited only at their endings on the surface of the body, while the efferent fibres are excited only at their origin from the spinal cord. The difference in the function of different nerve fibres depends therefore not so much on the structure of the nerve fibre itself as on the connections of the fibre. We can show this experimentally by grafting one set of nerve fibres on to another. If the cervical sympathetic be united to the lingual nerve, stimulation of the sympathetic, instead of causing as usual constriction of the vessels of the head and neck, will cause dilatation of the vessels of the tongue and secretion of watery saliva. In the same way the finer functional differences between the various forms of sensory nerves seem to be determined by their connections within the central nervous system. Stimulation of the optic nerve by any means whatsoever evokes a sensation of light. One and the same stimulus applied to different nerves will evoke different sensations, *e.g.* a tuning-fork applied to the skin will give a sensation of vibration, to the ear a sensation of sound. We shall have occasion to return to this question of the restricted function of nerve fibres when we deal with Müller's 'law of specific irritability' in the chapter on Sensation.

Changes in the Nerve during Transmission. In muscle we saw that the passage of an excitatory wave was accompanied or followed by electrical changes, production of heat and mechanical change, all pointing to an evolution of energy from the explosive breaking down of contractile material.

In nerve, which serves merely as a conducting medium, we should not expect so much expenditure of energy. All that is necessary is that each section of the nerve should transmit to the next section just so much kinetic energy as it has received from the section above it. The most evident change in a nerve under these circumstances is the development of a current of action. A nerve becomes, when excited at any point, negative at this point to all other parts of the nerve and, just as in muscle, this 'negativity' is propagated in the form of a wave in both directions along the nerve.

If we connect a galvanometer to two points of an uninjured nerve, no current is observed, all points of a living nerve at rest being isoelectric. On making a cross section of the nerve at one leading off point, a current is at once set up, which passes from the surface through the galvanometer to the cross section. This is a demarcation current, set up at the junction between living and dying nerve. This current rapidly diminishes in strength and finally disappears, owing partly to the fact that the dying process started in the nerve by the section extends only as far as the next node of Ranvier and there ceases, so that after a short time the electrode applied to the cross section is simply leading off an intact living axis cylinder through the dead portion of the nerve, which acts as an ordinary moist conductor. On making a fresh section just above the previous one, the process of dying is again set up, and the demarcation current is restored to its original strength. If, while the demarcation current is at its height, we stimulate the other end of

the nerve with an interrupted current, the needle of the galvanometer swings back towards zero, *i.e.* there is a monophasic variation.

In order to demonstrate the wave-like progression of the electrical change from the excited spot along the nerve, it is necessary, as in the case of muscle, to make use of a very sensitive capillary electrometer, string galvanometer or oscillograph. It is then found that the change progresses along the nerve at the same rate as the nervous impulse, *i.e.* 28 to 33 metres per second in the frog. But it lasts only an extremely short interval of time at each spot, viz. six to eight ten-thousandths of a second. Thus the length of the excitatory wave in nerve is about 18 mm. When by prolonged stimulation the nerve is thrown into protracted activity, a study of these action potentials indicates that the excitatory changes in the nerve fibre are *interrupted*, not continuous, even though the stimulus which gives rise to them may be quite continuous. We may compare the passage of such a stream of nerve impulses to the discharge of a stream of machine-gun bullets, rather than to the flow of a stream of water; 'continuous' activity of the fibre being represented by a quick succession of these short waves (Fig. 108). Adrian

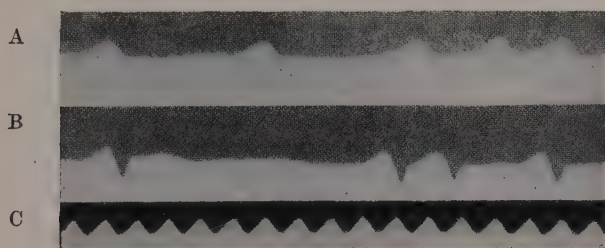


FIG. 108. Records by Oscillograph of Action Potentials produced in nerve by continuous stimulation of sensory endings in a toe muscle of the frog by means of a weight.

A = nerve injured (monophasic).

B = nerve intact (diphasic).

C = time trace 200 d.v. per second. (MATTHEWS.)

and Zotterman, for example, were able to show streams of impulses passing up the sensory nerves, from the pad of the cat's foot when this was subjected to pressure or other cutaneous stimulation, and Adrian and Matthews showed similar effects in the optic nerve of the eel when the eye was exposed to light. These researches indicate that the normal impulses travelling along sensory nerves are of the same nature as those which normally travel down the motor nerves. The more powerful the stimulus the more frequent the impulses which result from it; these impulses are all of the same size whether the stimulus be strong or weak.

That the excitatory process in nerves is probably dependent on certain small chemical changes is indicated by the facts that, in the complete absence of oxygen, the nerve fibres lose their irritability, and that this loss of irritability is hastened by repeated stimulation of the nerve. When the irritability has been abolished by stimulation in the absence of oxygen, it may be restored within a few minutes by readmission of oxygen to the nerve. Recent researches by A. V. Hill and his pupils have shown that small amounts of heat are produced when a nervous impulse traverses a nerve. The quantity of heat set free during the activity is minute (about 10^{-7} calories per impulse per gram of nerve) and is followed by the liberation, slowly, of a further amount eight to ten times as large (delayed heat).

Nerve continually uses oxygen and evolves carbon dioxide ; in the absence of oxygen, lactic acid accumulates, as it does in muscle, and on re-admission of oxygen, disappears again, with increased oxygen usage. When the nerve is stimulated, the rate of oxygen usage is accelerated (Gerard). These various facts indicate that the propagation of the nervous impulse is no passive process like the transmission of a merely physical commotion would be, but that the impulse is passed from point to point by an active participation of the fibre, inasmuch as it involves both heat production and chemical change. Many other facts are in complete accord with this belief.

CONDITIONS AFFECTING THE PASSAGE OF A NERVOUS IMPULSE

TEMPERATURE. Below a certain temperature the propagation of the excitatory process in the nerve is absolutely abolished. The exact tempera-

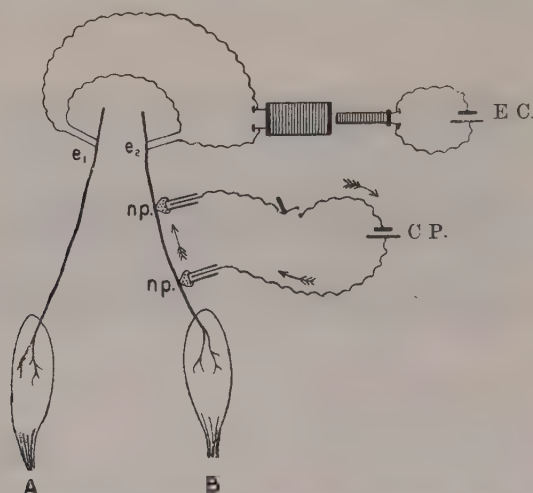


FIG. 109. Arrangement of Experiment for demonstrating the Absence of Fatigue in Medullated Nerve Fibres.

E.C., exciting circuit ; C.P., polarising circuit.

ture at which this occurs varies according as we use a warm- or a cold-blooded animal. In the frog it is necessary to cool the nerve below 0° C. before conduction is abolished, whereas in the mammal it is sufficient to cool the nerve to somewhere between 0° and 5° C. Since cooling the nerve does not excite it, this procedure forms a convenient method for blocking the passage of impulses along a nerve without using the irritating procedure of section. On again warming the nerve the conductivity returns. The rapidity with which the excitatory process is propagated along either a nerve or a muscle fibre depends on the temperature. Thus the mean rate of conduction in the frog's nerve at 8° to 9° C. is about 16 metres per second. The temperature coefficient of the velocity of nerve propagation, *i.e.* $\frac{\text{velocity at } T_n + 10}{\text{velocity at } T_n}$ has been found by Keith Lucas to be about 1.79.

THE INFLUENCE OF FATIGUE. In the description of the phenomena of muscular fatigue given in the last chapter, it was assumed that the muscle was being excited directly. The same phenomena are observed when the muscle is excited through its nerve, though in this case

fatigue comes on much more quickly. If, after the muscle has been excited in this way until exhausted, it be excited directly, it will respond with a contraction nearly as high as at the beginning of the experiment. Yet it is not possible to demonstrate any phenomena of fatigue in the nerve trunk.* This fact can be shown in *mammals* by poisoning the animal with curare, and then stimulating a motor nerve continuously while the animal is kept alive by means of artificial respiration. As the effect of the curare begins to wear off in consequence of its excretion, the muscles supplied by the stimulated nerve enter into tetanus. The action of the curare may be cut short at any time by the injection of salicylate of physostigmine, when the muscles will at once begin to react to the excitation.

The same fact may be shown on the excised nerve muscle preparation of the frog. The gastrocnemii of the two sides with the sciatic nerves are dissected out, and an exciting circuit is so arranged that the interrupted secondary currents pass through the upper ends of both nerves in series (Fig. 109). At the same time a constant cell is connected with two non-polarisable electrodes (*np*, *np*) placed on the nerve of B, so that a current runs in the nerve in an ascending direction. The effect of passing a constant polarising current through a nerve is to block the passage of impulses through the part traversed by the current. The exciting current is then sent through both nerves by the electrodes e_1 and e_2 . The muscle A enters into tetanus, which gradually subsides owing to 'fatigue.' When A no longer responds to the stimulation, the constant current through the nerve of B is broken. B at once enters into tetanus, which lasts as long as the contraction did in the case of A, and gradually subsides as fatigue comes on. Since both nerves have been excited throughout, it is evident that the fatigue does not affect the nerve trunk. We have already seen that a muscle will respond to direct stimulation when stimulation of its nerve is without effect, and must therefore conclude that the phenomena of fatigue are due to failure of the excitatory process to be transmitted from the nerve to the muscle.

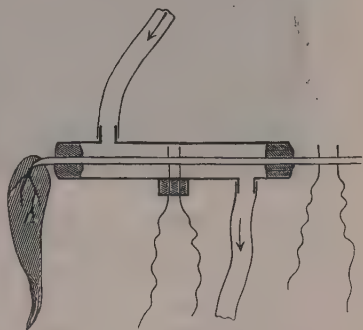


FIG. 110.

The failure of transmission is explained by Lapicque as being similar to that effected by curare. The chronaxie of the muscle steadily increases, while the nerve, apart from an increase of the rheobase, shows no change; when the chronaxie of the muscle reaches a value double that of the nerve the conduction is abolished, *i.e.* fatigue is apparently complete. On allowing the muscle to rest its chronaxie falls again, and its indirect excitability reappears.

In the normal intact animal the break in the neuro-muscular chain, which is the expression of fatigue, occurs still higher up, *i.e.* in the central nervous system, and is probably due to some reflex inhibition of the central motor apparatus from the muscle itself. Thus after complete fatigue has been produced in a muscle so far as regards voluntary efforts, direct stimulation of the muscle itself or its nerve will produce a contraction as great as would have been the case at the beginning of the experiment.

THE INFLUENCE OF DRUGS. The most important drugs with an influence on nerve fibres are those belonging to the class of anæsthetics. Of these we may mention carbon dioxide, ether, chloroform and alcohol.

The action of any of these substances on the excitability and conductivity of a nerve may be studied by means of the simple apparatus represented in Fig. 110. The nerve

* Unless it be asphyxiated by total deprivation of oxygen.

of a nerve muscle preparation is passed through a glass tube which is made air-tight by plugs of normal saline clay surrounding the nerve at the two ends of the tube. By means of two lateral tubulures, a current of CO_2 or air charged with vapour of ether or other narcotic can be passed through the tube. The nerve is armed with two pairs of electrodes which are stimulated alternately, the pair within the tube serving to test the action of the drug on the *excitability*, while the pair outside the tube show the presence or absence of any effect on the *conducting power* of the nerve below it.

Of the gases and vapours mentioned above, CO_2 and ether both diminish and finally abolish the excitability and conductivity of the nerve fibres. The conductivity however persists after all trace of excitability has disappeared, before in its turn being also abolished. On removing the gas or vapour by blowing air over the nerve, the conductivity and excitability gradually return in the reverse order to their disappearance (Fig. 111).

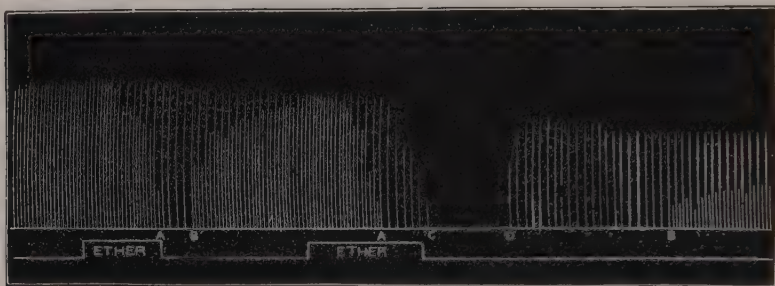


FIG. 111. Tracing to show the Effect of Ether on Excitability and Conductivity of Nerve. Nerve excited by single induction shocks alternately inside and outside ether chamber.

The vertical lines indicate contractions of the muscle (gastrocnemius.)

The lower line indicates the periods during which the nerve was exposed to the action of ether.

A, disappearance of *excitability*; B, reappearance of *excitability*; C, disappearance of *conductivity*; D, reappearance of *conductivity*. (GOTCH.)

Alcohol is said to increase the excitability or leave it unaffected, while diminishing the conductivity of the nerve.

Chloroform rapidly abolishes both excitability and conductivity, and in many cases its effects are permanent.

THE EXCITATION OF NERVE FIBRES

Many other different forms of stimuli may be used to arouse the activity of nerve. Thus we may use thermal, mechanical or chemical stimuli. If the temperature of a motor nerve be gradually raised, no effect is noticed till about 40°C . is reached, when the muscle may enter into weak quivering contractions. Sudden warming of the nerve always gives rise to excitation. At about 45°C . the nerve loses its irritability and dies. On the other hand a nerve may be rapidly cooled without any excitation taking place.

A nerve may be excited mechanically by crushing or cutting. These methods destroy the nerve. It is possible to excite a nerve mechanically, without any serious injury to it, by carefully graduated taps.

All chemical stimuli applied to the nerve have a speedy effect in destroying its irritability. The chemical stimuli most used are strong salt solutions, glycerin or weak acids. If any one of these be applied to a motor nerve, the muscle enters into an irregular tetanus, which lasts till the irritability of the nerve is destroyed at the part stimulated.

None of these forms of stimuli can be adequately controlled either as to strength or duration. Moreover, owing to their destructive effects, any

repetition of the stimulus will fall on a nerve or muscle more or less altered by the first stimulus. We are therefore justified in the use of electrical stimuli. For this purpose we may use either the make and break of a constant current, the induced current, or the discharge of a condenser. A nerve cannot be excited by currents passed transversely across it, the threshold for stimulation being inversely proportional to the cosine of the angle between current and nerve ($\cos. 90^\circ = 0$).

ELECTROTONUS. Under normal circumstances, if a constant current be passed through the nerve of a nerve muscle preparation for a short time, the muscle responds only at the make and the break of the current, remaining quiescent all the time the current is passing. If the nerve be in a very excitable condition, it is possible that the muscle may be thrown into a tetanus or continued contraction during the whole time that a *descending* current is passing ('closing tetanus'). On the other hand, if a strong *ascending* current be passed through the nerve for a considerable time, the muscle when the current is broken may go into continued contraction, which may last some time. Normally the muscle simply responds with a single twitch at the make and break of the current, although, on investigating the condition of the nerve *during* the passage of the current, we find that it is considerably modified. This modification in the condition of the nerve is spoken of as *electrotonus*, and includes changes in its irritability and its electrical condition.

To investigate these changes the following apparatus is necessary: a galvanic battery, induction coil, a reverser and keys, a pair of non-polarisable electrodes, and a pair of ordinary platinum electrodes. Fig. 112 represents roughly the arrangement of the apparatus. A constant current from the battery is led through a part of the nerve by means of non-polarisable electrodes, which are about one inch apart. In this circuit we put a reverser, by means of which the direction of the current through the nerve may be changed at will, and a key to make or break the current. This is the polarising circuit. The coil, with key and cell in the primary circuit and short-circuiting key in the secondary (not shown in the figure), is arranged so that we may use, make or break induction shocks, which are applied to the nerve by means of the small platinum electrodes. The tendon of the muscle is connected to a lever, which writes on a smoked surface.

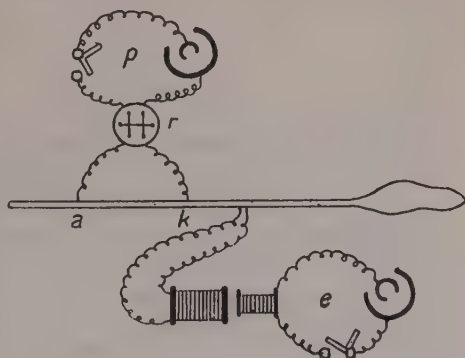


FIG. 112. Arrangement of Apparatus for showing Electrotonic Changes in Excitability.
e, exciting current; p, polarising current;
r, Pohl's reverser.

We first find the position of the secondary coil, at which the break induction shock is submaximal, and we employ this strength of stimulus throughout the experiment. The make induction shock is prevented from acting on the nerve by closing a short-circuiting key in the circuit of the secondary coil. The nerve is now stimulated at various points with a single break induction shock. The heights of the contractions serve to indicate the excitability of the nerve at the point stimulated. We now throw a descending polarising current into the nerve. At the make of this current the muscle will probably respond with a twitch which is not recorded. We then test once more the irritability of different points of the nerve, and we find that when the stimulus is applied near the anode, the stimulus, which before gave a moderately large contraction of the muscle, now has little or no effect. On the other hand, in the region of the cathode the stimulus, which before was submaximal, has now become maximal, as shown by the increase in the height of the contraction evoked by the induction shock.

We now reverse the direction of the polarising current, so that the current in the nerve is ascending. With this reversal of current there is also a reversal of the changes in the nerve: that is to say, the normally submaximal stimulus is again maximal when applied near the cathode, and minimal when applied near the anode. On break of the polarising current the condition of the nerve returns to normal, and the submaximal stimulus is once more submaximal throughout.

This return to normal conditions is not immediate, since the first effect of breaking the current is a swing back, so to speak, past the normal, the diminished irritability at the anode giving place to an increased irritability which only gradually subsides. In the same way, immediately after the polarising current has ceased to flow, the neighbourhood of the cathode acquires a condition of diminished irritability, and this only gradually gives place to a normal condition.

This experiment teaches us that, when a constant current is passed through a nerve, there is an increase in the excitability in the nerve near the cathode, and a diminution in excitability near the anode. These conditions of increased and diminished irritability are spoken of as *catelectrotonus* and *anelectrotonus* respectively. In muscle we have seen that a make contraction always starts from the cathode, and a break contraction from the anode. Now the event that takes place at the cathode on make and at the anode on break of a constant current is, as the last experiment shows us, a rise in

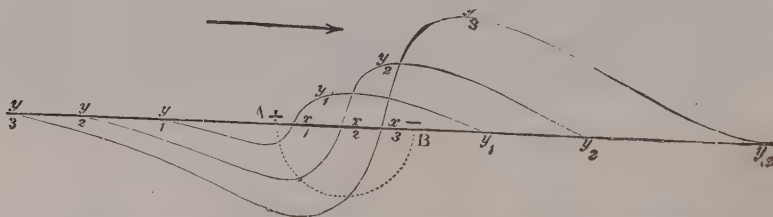


FIG. 113. Diagram to show the Variations of Excitability in a Nerve during the Passage of Polarising Currents of different Strengths. The degree of change is represented by the distance of the curves from the base line; the part of the curve below the line signifying decrease, that above the line increase of irritability.

A, anode; B, cathode; y_1 , effect of weak current; y_2 , medium current; y_3 , strong current. It will be noticed that the indifferent point, x , where the curve crosses the horizontal line, approaches nearer and nearer the cathode as the current is increased in strength. (From FOSTER, after PFLÜGER.)

irritability, in the former case from normal to above normal, in the latter from subnormal to normal. Hence we may say that the excitation by a galvanic current is caused by a sudden rise of irritability, which may be due either to a sudden appearance of catelectrotonus or a disappearance of anelectrotonus. I have said sudden because the steepness of the rise of irritability is a necessary factor in causing excitation. If the polarising current passing through a nerve be slowly and gradually increased to considerable strength, it will give rise to no contraction. The degree of suddenness of the rise, which is most beneficial in causing contraction, varies with the nature of the tissue stimulated. Thus it is more rapid in nerve than in muscle, in pale muscle than in red muscle, and in voluntary muscle than in unstriated muscle.

There must be, somewhere between the anode and cathode, an indifferent point—that is to say, a region where the irritability is neither increased nor diminished. We find experimentally that this indifferent point is nearer the anode when the polarising current is weak, and approaches the cathode as the current is strengthened, so that with very strong currents nearly the whole intrapolar length is in a condition of anelectrotonus (Fig. 113). When a strong polarising current is used, the depression of irritability at the anode is so marked that no impulse can pass this region. Thus if we send a very strong ascending current through the nerve, there is

no contraction at make. This is owing to the fact that the impulse started at the cathode on make of the current cannot reach the muscle, its passage down the nerve being blocked in the region of the anode (Fig. 114, A). Similarly at break of a strong descending current, the excitation originating at the anode is blocked by the great depression at the former cathode (Fig. 114 B).

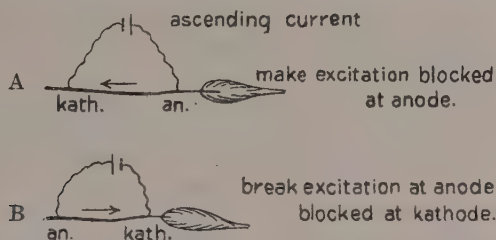


FIG. 114. Diagram to show the Blocking Effect of a strong Constant Current passed through the Nerve of a Nerve-muscle Preparation.

The results of stimulating motor nerves by means of constant currents were studied by Pflüger and make up what is known as Pflüger's law. The effects of the currents depend on their strength and direction.

LAW OF CONTRACTION

Strength of Current.	Ascending		Descending	
	Make	Break	Make	Break
Weak	c	O	c	O
Medium	c	c	C	c
Strong	O	C or T	C or T	O

c = contraction. C = strong contraction. T = tetanus. O = no effect.

With the weakest currents excitation occurs only at make, since a make stimulus *i.e.* the rise of catelectrotonus, is always more effectual than a break stimulus, *i.e.* the disappearance of anelectrotonus. With currents of moderate strength excitation occurs both at make and break, being better marked at make especially in the case of descending currents. With very strong currents we get a contraction at make only when the current is descending since, when the current is ascending, the excitation started at the cathode cannot pass the block at the anode. For a similar reason a break contraction is obtained only with an ascending current since, at the break of

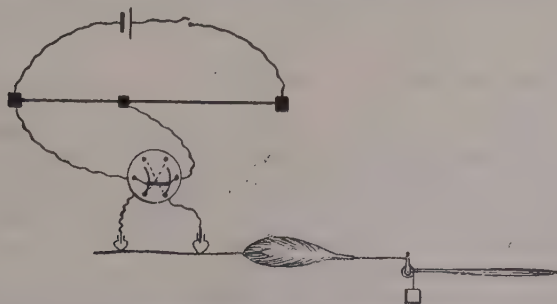


FIG. 115. Arrangement of Experiment to demonstrate Pflüger's Law of Contraction.

a descending current, there is a swingback of the nerve at the cathode to a condition of diminished irritability, which effectually blocks the excitation started higher up the nerve at the anode.

The arrangement of the experiment for demonstrating Pflüger's law is shown in Fig. 115. The strength of the current is graduated by means of the rheochord, the

current being led into the nerve by means of non-polarisable electrodes. It is extremely important in these experiments to avoid any injury or drying of the nerves at either of the two electrodes, since the excitatory effect at make or break would be abolished by local injury.

It is said that an anelectrotonus takes some time to attain its full height, and a catelectrotonus reaches its maximum almost directly after the current is made.

These results, worked out chiefly on motor nerves, have been confirmed as far as possible experimentally on sensory nerve, and probably hold good for all irritable tissues.

Other things being equal, a current of given strength causes a stronger excitation the greater the length of nerve (up to 20 mm.) that it flows through. It must be remembered however that the nerve offers considerable resistance

to the passage of the current and so, to keep the current constant while increasing the length of intrapolar nerve, we must largely increase the electromotive force employed.

A very convenient method of showing the effect of the length of intrapolar nerve on excitation was suggested by Gotch. The two sciatic nerves of a frog are dissected out, one of them being in connection with the gastrocnemius. These are first arranged as in Fig. 116, A. *a*, *b* and *c* are three non-polarisable electrodes, the terminals of a constant battery being connected to *a* and *c*. The position of the rider on the rheochord is then ascertained at which make of the current just excites contraction in the muscle of nerve 2, the current in this case passing from *a* to *b* along nerve 1,

and from *b* to *c* along a small piece of

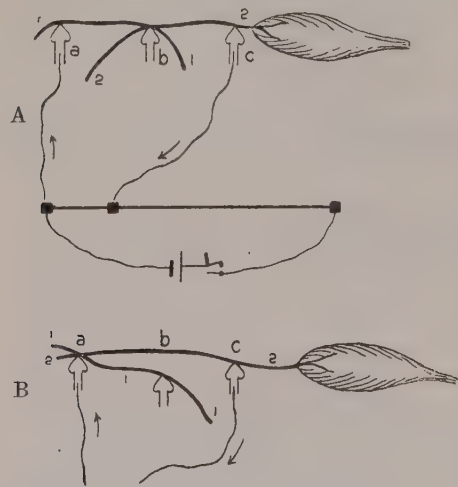


FIG. 116.

nerve 2. We will suppose that eleven units of current are necessary to produce excitation. *b* is then withdrawn and the nerve 2 laid on *a* (Fig. 116, B), so that the current can now pass from *a* to *c* entirely through a long stretch of nerve 2. On again seeking the minimal stimulus, it will be found that a smaller current is sufficient to excite, contraction being obtained with seven units. Since the length of nerve traversed, and therefore the resistance to the current, are the same in both cases, it shows that a current is more effective the greater the length of nerve that it traverses.

ELECTRICAL STIMULI AS APPLIED TO HUMAN NERVES

When we attempt to apply the results gained on frog's nerves to man, we are met at once by the difficulty that we cannot dissect out the nerves and apply stimuli to them directly. So usually *unipolar* excitation is used, a small, or stigmatic electrode, either anode or cathode, being applied to the skin over the nerve to be stimulated, and the other, a large one, to some indifferent point, such as the back. Under these circumstances the current is concentrated as it leaves the stigmatic electrode, and diffuses widely in the body, seeking the lines of least resistance. Thus it is impossible to get pure anodic or cathodic effects. If the anode be applied over the nerve, the current enters by a series of points (the polar zone), and leaves by a second series (the peripolar zone). The polar zone will thus be in the condition of anelectrotonus, and the peripolar zone in that of catelectrotonus. The current however will be more concentrated at the polar than at the peripolar zone,

and so the former effect will predominate. These restrictions in the application of the current cause slight apparent irregularities in the law of contraction as tested on man.

In stimulating the nerves of man for the purpose of determining the conditions of the different muscles, we may use either induced currents (generally called faradic stimulation) or the make and break of a battery current (galvanic stimulation). The electrodes are covered with chamois leather moistened with salt solution in order to diminish the resistance of the skin. When it is desired to stimulate any given muscle, the stigmatic electrode is brought as nearly as possible over the spot where the muscle receives its motor nerve. These 'motor points' have been mapped out, and reference is generally made to a diagram in determining the point for any given muscle. By reversing the current the stimulating electrode may be made either anode or cathode. It is found that stimulation occurs most easily on closure of the current when the stimulating electrode is the cathode; with the greatest difficulty when the current is broken and the stimulating electrode is the cathode. These different contractions are generally repre-

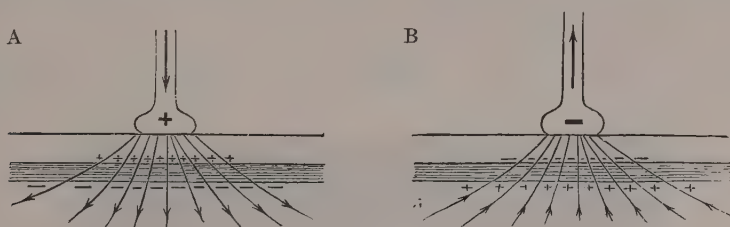


FIG. 117. Electrodes applied to the Skin over a Nerve Trunk.

In A the polar area is anelectrotonic and the peripolar catelectrotonic. The former condition preponderates, since the current here is more concentrated. In B the conditions are reversed, the polar zone corresponding in this case to the cathode. (WALLER.)

sented by capital letters, and the usual relationship is expressed by the statement that CCC is obtained most easily, then ACC and AOC, and finally COC.

CCC = cathodal closing contraction.
 ACC = anodal closing contraction.
 AOC = anodal opening contraction.
 COC = cathodal opening contraction.

The problem of the determination of the chronaxies of the human nerves or muscles has been very thoroughly investigated by Bourguignon, who made the important observation that different muscles (with their nerves) have different chronaxies, and further, that in the same segment of a limb, muscles of similar function have the same chronaxie. Thus when the chronaxie of flexor and extensor muscles is compared it is found that the flexors have a chronaxie only half as great as the extensors. This agrees with the relative duration of the contractions, which Baird and Fulton find to be about 30 σ and 40 σ respectively.

When the motor nerve to a muscle has undergone degeneration, the muscle also begins to degenerate, and we find certain alterations in its chronaxie. For some time after section of the motor nerve the chronaxie of nerve and muscle remains unaltered; this period may be up to a week or ten days in the sciatic-gastrocnemius of the frog, and at the end of this time the nerve has ceased to function. The chronaxie of the muscle then steadily increases, and at the end of three months is up to five times its normal value. In warm-blooded animals and in man the change takes place much more rapidly.

The muscle after degeneration of its nerve gives a slow contraction and is frequently of such high chronaxie as to be inexcitable to the brief faradic shock (reaction of degeneration). In the second place, qualitative alterations in irritability may be present, so that ACC may be obtained with a smaller current than CCC. Changes in the chronaxie are, however, detectable long before this stage is reached.

REFRACTORY PERIOD AND SUMMATION OF STIMULI.

The phenomenon of a refractory period seems to be common to all excitable tissues. Thus if two 'adequate' stimuli are applied to a nerve within a

sufficiently brief interval, the second stimulus is ineffective, so far as can be determined by the response of an attached muscle or by means of a capillary electrometer. The period is longer the lower the temperature and varies from 0.6σ at 40°C. to 3.0σ at 12°C. This critical interval is lengthened if the irritability of the nerve is depressed by narcotics.

The period of diminished irritability immediately after the application of a stimulus is succeeded by one during which the nerve is more excitable. The same phenomena are found when not the excitability but the conductivity of a nerve is investigated. Thus in a frog's sciatic nerve at 15°C. :

Conduction is impossible from 0 to 0.003 sec. after a previous impulse.

Conduction is impaired from 0.003 to 0.015 sec. " " "

Conduction is supernormal from 0.015 to 0.1 sec. " " "

(Keith Lucas.)

The summation of two *inadequate* stimuli is possible in a nerve, provided these are not more than 0.5σ apart.

THE EFFECT OF TEMPERATURE ON EXCITABILITY. It was found by Gotch that the threshold of excitability of a nerve within

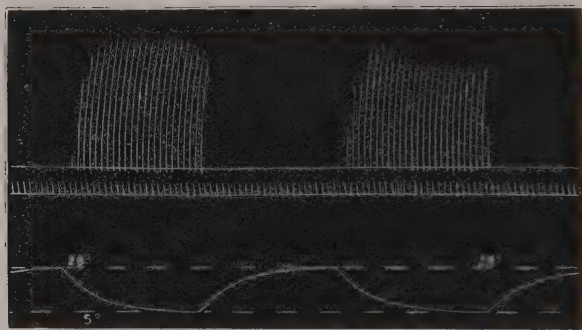


FIG. 118. Tracing of Muscle Contractions to show Effect of Cooling a Nerve on its threshold of Excitability.

The lower line indicates the changes in temperature of the excited part of the nerve. The muscle responded only when the nerve was cooled, the stimulus becoming ineffectual when the nerve was warmed. (GOTCH.)

certain limits was lowered by cooling the nerve and increased by raising its temperature (Fig. 118). Thus if a frog be cooled to 2°C. or 3°C. for a day, it will be found that simple section of the sciatic nerve may suffice to send the gastrocnemius into continued contraction, and under these circumstances 'closing tetanus' may be obtained with the greatest ease. This increase of 'excitability' does not however imply a diminished chronaxie, but only a reduced rheobase. Actually the chronaxie of both nerve and muscle are increased by cooling, and therefore they are *less* excitable for induction shocks and for galvanic currents of short duration.

THE EFFECT OF INJURY. The irritability of the nerve of a nerve-muscle preparation is not equal in all parts of its course but is greater at the upper end, probably because it is nearer to the site of injury.

Some time after a motor nerve is divided, the increased irritability at the upper end gives way to a decreased irritability, and this decrease goes on till the nerve is no longer excitable. The diminution in excitability gradually extends down the nerve fibre, so that the part of the nerve nearest the muscle remains excitable the longest (the Ritter-Valli law). It is soon followed by definite histological changes in the nerve.

THE NEURO-MUSCULAR JUNCTION

The excitatory process travelling down a motor nerve has to be transmitted to the muscle by the intermediation of the nerve ending or end plate. We have learnt to regard the axis cylinder as the seat of the propagated excitatory process. In the end plate however the axis cylinder comes to an end. When stained by methylene blue or by impregnation with chromate of silver or mercury, the axis cylinder, after passing through the sarcolemma of the muscle fibre, is seen to break up into a number of branches (in some cases forming a typical end-arborisation), which lie on or are embedded in a small amount of undifferentiated protoplasm containing nuclei (the 'sole plate'). A similar break in structural continuity seems to occur in the central nervous system wherever an impulse is propagated from the axon process of one nerve cell to the body or dendrites of another nerve cell, and the area of contiguity, where an impulse passes from one neuron to another, is spoken of as a *synapse*. The presence of the synapse, or end plate, between muscle and nerve imposes certain new conditions on the conduction of the excitatory impulse. One of the most important of these lies in the fact that the conduction across the end plate, and probably across the synapse of the central nervous system, is *irreciprocal*. An excitatory process started in the nerve travels easily across the end plate to the muscle. On the other hand an excitatory process started in the muscle does not extend through the end plate to the nerve fibre. This fact may be shown on the frog's sartorius. If the lower tibial end of the muscle be split, as in Fig. 119, a mechanical stimulus, such as a snip with the scissors, applied to the lower nerve-free end of one of the limbs, e.g. at A, causes a contraction of the corresponding half of the muscle which does not extend to the other half. On snipping the muscle a little higher up at B, where nerve endings are present, the resulting contraction involves the whole of the muscle, owing to the fact that the excitation started in the nerve endings spreads in both directions through the branching nerve fibres.

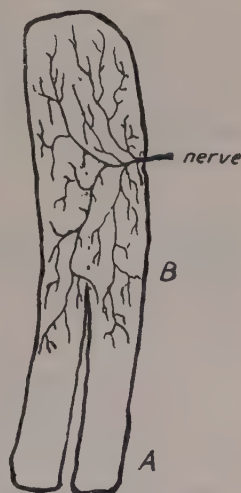


FIG. 119.

There is evidence that the transmission of the excitatory condition across the end plate from nerve to muscle involves a special excitatory process and the expenditure of energy. Thus there is a period of delay between the arrival of an excitatory impulse at the terminations of the motor nerve and the beginning of the electrical change which marks the moment of stimulation of the muscle fibre. If we compare the latent period of a muscle stimulated directly with its latent period when excited through the nerve, we find that there is an increased period of delay in the latter which is not wholly accounted for by the time taken for the impulse to travel from the stimulated spot down the nerve fibres to the muscle. The extra delay is due to the processes occurring in the end plate, and amounts to 3 to 4 σ . It is possibly due to the fact that the conduction of the excitatory state becomes slower and slower as the branching fibres become finer. The end plate seems to be the weakest point in the neuro-muscular chain. We have already seen that, when the nerve of a nerve-muscle preparation is stimulated repeatedly, the muscle very soon shows signs of fatigue, and that the seat of this fatigue is not in the nerve nor in the muscle, but at the junction between the two, and

we have seen that there is evidence that this is due to a discrepancy in the chronaxies of the nerve and the muscle, similar to that induced by curari.

It has been suggested that the excitation of muscle through nerve depends on an electrical change or discharge at the nerve ending. This discharge must originate in the terminations of the axon and must influence the contractile material of the muscle. It would be reasonable to suppose that when the chronaxie of the muscle is lengthened by fatigue or by the action of a drug such as curari, it becomes incapable of responding to the brief stimulus offered by the action current of the nerve.

In the visceral neuro-muscular system the nerve fibres leaving the central nervous system do not pass direct to the muscle fibres, but end in arborisations round ganglion cells, which are collected to form the ganglia of the sympathetic chain or ganglia situated more peripherally and nearer the reacting tissue. Relays of fibres, for the most part non-medullated, arise from these ganglion cells and pass to the unstriated muscles of the blood vessels and viscera, where they end in plexuses or networks among the muscle fibres, possibly connected by short branches with the fusiform muscle fibres themselves. No structure is present at the periphery exactly analogous to the end plate, and it is possible that, as Elliott suggests, the end plate is really homologous with the whole of the sympathetic ganglion with its post-ganglionic fibres passing to the visceral muscles.

The investigations of Elliott on the action of adrenaline furnish good grounds for the belief that, in plain muscle at all events, there is some intermediary substance, the myoneural junction between nerve and muscle tissue. Adrenaline apparently does not act direct on the plain muscle cell; yet after section and degeneration of the nerve, the motor action of adrenaline is retained, if not augmented; certainly after removal of the superior cervical ganglion the effect in causing dilatation of the pupil of minute amounts of adrenaline is greatly increased.

POLARISATION PHENOMENA IN NERVE

ELECTROTONIC CURRENT. If a constant current be passed through a nerve fibre through the electrodes *x* and *y*,—*x* being the anode and *y* the cathode—and the extrapolar portions of the nerve *ab*, *cd*, be connected with galvanometers, the needles of both are deflected, and the direction of the deflection shows the existence of a current in the extrapolar portions of the nerve from *a* to *b*, and from *c* to *d* (Fig. 120).

We thus see that passage of a current through part of a nerve gives rise to a current flowing through a considerable portion of the nerve fibre on each side of the polarising current and in the same direction. This current is called the 'electrotonic current.' It must not be confounded with the 'current of action', which originates at one of the poles only at make or break of the current, and is transmitted thence in the form of a wave with a measurable velocity (in the frog) of about 30 metres per second. The electrotonic current is developed instantaneously, and lasts the whole time that the current is flowing through the nerve. It is caused by the occurrence of polarisation between the sheath and the conducting part of the nerve fibre, and may be exactly reproduced on a model. Although thus physical in origin, its production is dependent on the vitality of the nerve, and so is not to be confounded with a simple spread of current.

The polarisation phenomena resulting from the passage of a constant current through a medullated nerve can be studied on a model made up of a glass tube filled with normal salt solution, containing a platinum or zinc

wire stretched through it (Fig. 121). On leading a current through a and b , and connecting c and d with a galvanometer, a current will be observed in

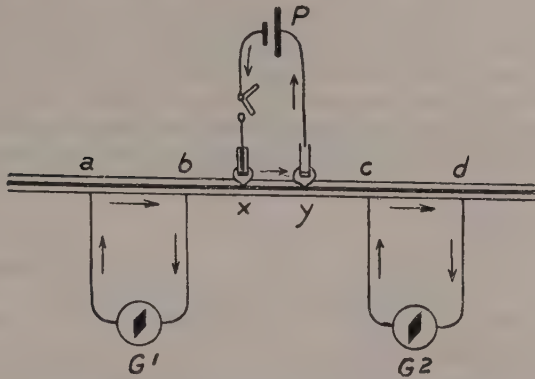


FIG. 120. Diagram showing Electrotonic Currents. P , polarising circuit; G^1 , G^2 , galvanometers.

The galvanometers will indicate, before the passage of the polarising current, the ordinary demarcation current of the nerve resulting from the cross section at the upper end. This current flows in the outer circuit from equator to cut end, and therefore in the nerve fibre from a to b , and from d to c . The effect of closing the polarising current will be to increase the current of rest between a and b , and to diminish that between c and d .

the extrapolar portion of the model in the same direction as in the intrapolar. That this spread of current is due to polarisation is shown by the fact that, if the model be made of zinc wire immersed in saturated zinc sulphate solu-

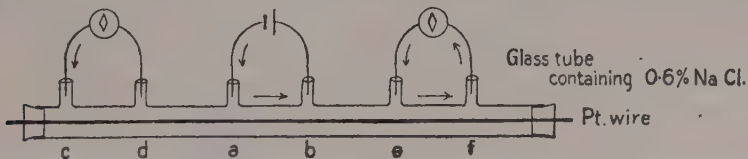


FIG. 121. Apparatus for imitating the Polarisation Phenomena in Medullated Nerve ('Kernleiter' model).

tion, so that no polarisation can occur, the spread of current to the extrapolar area is wanting. If we examine the phenomena taking place at the anode, we see that a current passes here through an electrolyte to the

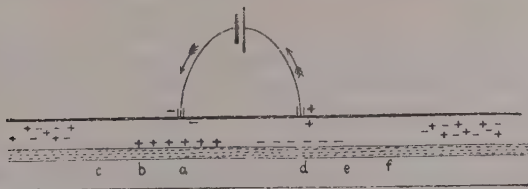


FIG. 122. Diagram to show Polarisation at the Surface between Conducting Core and Electrolyte Sheath in a 'Kernleiter.'

conducting core. Every current through an electrolyte is carried by ions. We get therefore a movement of negative ions up into the electrode, and a deposition of electropositive ions on the core (Fig. 122, a). In the same way at the cathode there will be a deposit of electronegative ions on the core (Fig. 122, d), so we may say that the core is positively polarised at the anode

and negatively polarised at the cathode. This polarisation, while opposing the primary current, will set up currents in the surrounding electrolytic sheath, as shown by the arrows in Fig. 123, the current passing from *a* to *b*, and from *b* to *c* in the electrolyte, returning towards *a* in the core. Hence if we lead off from the sheath in the neighbourhood of the anode from *a* and *c*, a current will pass in the galvanometer from *a* to *c*, and along the core in the same direction as the intrapolar current. The same factors will cause an extrapolar current in the cathodic area, the 'catelectrotonic current.'

This polarisation will not disappear at once on breaking the polarising

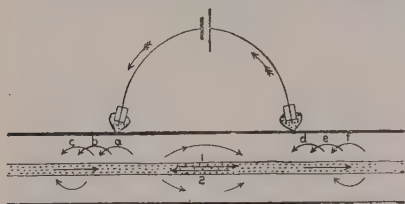


FIG. 123. Diagram to show Polarisation Currents in a 'Kernleiter,' or in a Medullated Nerve.

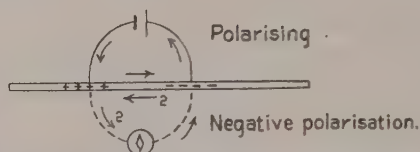


FIG. 124. Diagram to show Direction of the Negative Polarisation Current, accompanying a Break Excitation.

current. The nerve or nerve model will still be polarised positively at the anode and negatively at the cathode. On connecting therefore these two points with the galvanometer, we shall get a current through it in the direction opposite to the previous polarising current, viz. from anode to cathode (Fig. 124). This is the so-called *negative polarisation* of nerve. Similarly in the extrapolar regions of the nerve, we shall have currents in the *same* direction as the previous polarising current, as shown by the arrows. So far then the nerve behaves exactly like the mechanical model. If however we pass a very strong current through a nerve, and then quickly switch

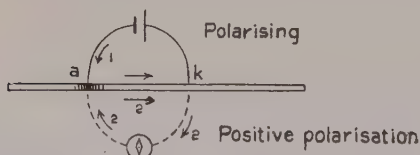


FIG. 125. Diagram to show Direction of the Positive Polarisation Current.

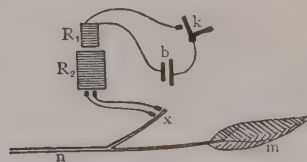


FIG. 126. Diagram of Arrangement for showing Paradoxical Contraction.

the nerve on to a galvanometer, we find a momentary current through the galvanometer in the same direction as the previous polarising current. This is known as *positive polarisation* of nerve. It is absolutely dependent on the living condition of the nerve, and is in fact an excitatory phenomenon due to the strong excitation which occurs at break of the current at the anode. Thus in the diagram (Fig. 125) a strong current is passing through the nerve from *a* to *k*. When this current is broken, excitation occurs, as we have already learnt, at the anode, and this excitatory state may, if the previous currents were strong, last two or three seconds. An excited tissue is however always galvanometrically negative towards adjacent unexcited tissue, and therefore if we connect *a* to *k*, there must be a current outside the nerve from *k* to *a* and in the nerve from *a* to *k*, viz. in the same direction as the polarising current. We see therefore that negative polarisation is due to polarisation occurring between an electrolytic sheath and a conducting core,

whereas positive polarisation is hardly a polarisation effect at all, but is a current of action.

PARADOXICAL CONTRACTION. If the sciatic nerve of a frog be dissected out, and one of the two branches into which it divides be cut, and the *central* end of this branch stimulated, the muscles supplied by the other half of the nerve contract to each stimulus. Ligature or crushing of the nerve *x* (Fig. 126) between the points stimulated and the point which joins the main trunk puts a stop to this effect, showing that it is not due to a mere spread of current. The fibres passing down *n* are in fact stimulated by the electrotonic current developed in *x* during the passage of the exciting current.

THE NATURE OF THE NERVE IMPULSE AND OTHER • PROPAGATED EXCITATIONS

Under this heading we have two questions to discuss: (*a*) the nature of the change aroused at the stimulated spot in an excitable tissue, and (*b*) the propagation of the excitatory change away from the stimulated spot, *e.g.* down a nerve fibre.

ALL-OR-NONE CHARACTER OF THE IMPULSE. We must regard the nervous impulse as some form of energy transmission, since it is capable on arrival at its destination of throwing its effector organ into activity. A very important question is that concerning the type of propagation to which the nervous impulse belongs. Is it transmitted passively along the conducting medium like a current of electricity or like sound, or does the nerve fibre contribute energy which keeps the impulse alive and transmits it from point to point, as, for example, in the travelling of combustion along a train of gunpowder?

In the former case the impulse must get progressively weaker as it travels along, and its damping down may, under certain conditions, be greatly accelerated, as, for example, that of sound in encountering a layer of cotton wool; in other words, the nervous impulse would normally suffer a decrement which might or might not be measurable, but from which, in its further passage along its course, it would never recover again.

In the latter case, the impulse would maintain a constant (all-or-none) intensity so long as the conditions were constant and, although its progress might be damped down locally, as in a stretch of burning fuse which had been moistened, it would, if it succeeded in emerging from such a region of depression, again flare up to its normal level.

Adrian came to the conclusion that, after having passed through a region of impaired conduction brought about by local narcosis, the nerve impulse did again spring up to its normal level on emerging into a normal stretch of nerve, and subsequent work has thoroughly substantiated this conclusion. That the nerve fibre shows all-or-none phenomena is also demonstrated by an experiment by Keith Lucas; he studied a single nerve fibre which supplied some twenty muscle fibres by branches of its axon and found that if a stimulus was applied to the nerve fibre, it either caused no contraction of any of the muscle fibres or contraction of all twenty, no grading being possible.

Adrain has pointed out that the all-or-none response of nerve is a logical consequence of its having a threshold of excitability and a refractory period. A stimulus in order to excite must produce a certain minimal local change and the propagated disturbance which is set up as soon as this change has reached its critical value, must therefore be of an all-or-none character.

stimulus beyond threshold strength "may cause the local change to exceed the value required for excitation, but the disturbance will have been set up at the moment when the critical value was reached, and the refractory state accompanying the disturbance will prevent any subsequent change in the local conditions from affecting its size in any way."

All experimental evidence shows that the greater effect produced by a stronger, as compared with a weaker stimulus applied to a nerve trunk, is due to the more rapid generation of nerve impulses in the fibres affected, and also to its spread to a larger number of nerve fibres, some of which are either less excitable, or by reason of their position less accessible to the stimulating agency than others.

THE NATURE OF THE EXCITATORY PROCESS. An attempt has been made by Boruttau and other physiologists to explain the nerve process, not as a wave of electrical change affecting the substance of the axis cylinder itself, but as a propagated catelectrotonic current. This observer found that, by working with a 'platinum core model' (Fig. 121) of considerable length, the catelectrotonic current was developed at one end of the model some appreciable time after a current had been sent in at the other end, thus resembling a current of action. It is however impossible to explain all the electrical phenomena of nerve as due simply to polarisation. Moreover the phenomenon of propagation of an excitatory process is equally well marked in tissues, such as muscle and non-medullated nerve fibres, which show very little of the electrotonic effects described in the last section. The all-or-none character of the impulse, together with the absence of decrement in the excitatory process has been taken as an indication that the axis cylinder of the nerve is the seat of energy changes which may be let loose under the influence of chemical or electrical changes, just as the energy of a contracting muscle is set free by the exertion of an infinitesimal force applied as a stimulus.

Against this view might be urged the absence of phenomena of fatigue in nerve. But this may possibly be explained by a continual process of restitution taking place at the expense of the sheath. Fatigue is absent, not because nothing is used up, but because the assimilative changes exactly balance and make good the dissimilation involved in the propagation of a nervous impulse.

There is thus some justification for the comparison of a nerve fibre to a chain of gunpowder, though in the nerve fibre the impetus to disintegration imparted from each particle to the next in order, is only accompanied by a very small rise in temperature, but principally by an electrical change. The excited condition at any segment of a nerve is associated with a development of electromotive forces at the junction of the segment with the adjacent resting segments. The current of action thereby produced can pass by the sheath of the nerve, so that it must enter the axon at the excited spot, and leave it at the adjacent unexcited segment. Hermann has suggested that in this way the current of action at any stimulated spot may excite the adjacent segments or molecules, causing them to become negative and thus setting up a current of action which in its turn excites the succeeding segments. In this way the excitatory process may travel the whole length of the nerve. Propagation would thus involve the successive setting up of an excitatory process all along the nerve or excitable tissue.

Though chemical changes no doubt accompany the activity of a nerve, the smallness of the energy changes involved in the transmission of an impulse forbids us to regard the body of the nerve as the seat of any considerable chemical change. It is much more probable

that the surface membrane, separating the axis cylinder from its surroundings, is the site of the propagated disturbance. If we suppose that this is only one molecule thick, it is evident that the amount of energy involved would be very small. If for instance the layer consisted of a monomolecular film of fatty acid on a nerve fibre 10μ in diameter, its volume would be only $\frac{1}{5000}$ of that of the nerve fibre. Thus the active element in a nerve fibre would be a monomolecular film of passive substance deposited and maintained on the nerve under the influence of the oxidative reactions which go on slowly and normally during life. Hinder the oxidation and the film breaks down so that the impulse can no longer be transmitted.

R. Lillie has drawn attention to the striking analogy between the nerve impulse and the change which can be propagated along an iron wire lying 'passive' in nitric acid. If such a wire be immersed in nitric acid of a specific gravity exceeding 1.2, it reacts only momentarily and then enters into a passive state in which no further solution occurs, a thin film of oxide being developed and maintained on its surface. Yet this seemingly stable system is highly reactive. Activation may be brought about by electrical, chemical or mechanical means. For example, if the wire is touched by a piece of zinc, it becomes activated at that spot, and turns black and effervesces; moreover, the activation thus initiated spreads as a wave of definite velocity over the whole surface of the wire, lasts for a few seconds, and disappears, the iron becoming passive again. But now the freshly passivated iron is resistant to re-activation for a minute or so (refractory period), after which the sensitivity to activation returns again. Mechanical stimulation, summation, electrotonus, polar stimulation on electrical activation, &c., can all be imitated on this fascinating model, as can also some of the facts of the time-relations of electric currents, such as the relative inefficacy of slowly rising currents to activate as compared with currents of abrupt onset. Thus the iron wire in these particular conditions transmits a self-propagating electrochemical change, limited to its surface film and in many respects analogous to the propagated impulse in a nerve.

BOOK III
THE CENTRAL NERVOUS SYSTEM
AND SPECIAL SENSES
(By H. HARTRIDGE, F.R.S.)

THE CENTRAL NERVOUS SYSTEM

CHAPTER XIV

GENERAL FEATURES OF A CENTRAL NERVOUS SYSTEM

EVERY vital phenomenon may be regarded as conditioned by some change in the environment of the animal and adapted to its preservation. In the whole organism, the defence of any one part must involve the co-operation of the whole. For this subordination of the activities of each part to the welfare of the whole a means of communication is necessary between the various parts. For some of the lower functions the channel of communication is the blood, which serves as a medium for carrying food material or chemical messengers. This method of correlating different activities would however be too slow and clumsy for the quick adaptation of the organism to sudden changes of environment. Such a rapid correlation can be effected only by a propagation of some swift message from the seat of incidence of the stimulus, either to all parts of the body or to some mechanism controlling all parts of the body. This is furnished by the nervous system. We have seen that stimuli of various kinds are transformed by a muscle or nerve fibre into what we call a state of excitation, which is propagated along such fibres at a certain definite rate, its passage in the case of the muscle being followed by a wave of contraction.

In unicellular animals, such as the *amœba* and *vorticella*, there is no differentiation of any structure which can be regarded as peculiarly nervous. A stimulus applied to any part of the *amœba* may evoke responsive activity in all other parts. A slight touch applied to any point on a *vorticella* will cause an excitation which is rapidly propagated to the stalk, causing this to contract and so withdraw the organism from any possible injury. In the lowest metazoa, such as the sponges, we find no special nervous structures. The cells forming the sponge may react to changes in their environment by contraction or by alteration of their relative positions. Many of the cells can move from one part of the sponge to the other in response to chemical changes occurring in the body of the sponge. So far, however, no cells have been distinguished as endowed above their fellows with the property of irritability or the power of reaction to stimulus. It is in the next class, that of the *cœlenterata*, where we first find a definite nervous system. The object of a nervous system is to ensure the co-operation of the whole organism in any reaction to changes in its surroundings. At its first appearance, therefore, we should expect a nervous system to be developed in connection with that layer of the animal which is in immediate relation to the environment, namely the *epiblast* or external layer. In some species of *hydra*, though no typical nervous tissues have been detected, many of the epithelial cells lying on the surface are prolonged at their inner ends into a long contractile process (Fig. 127, A), so that stimuli applied to the surface and acting on the epithelial cells can cause, as an immediate response, a contraction of the underlying muscular processes. We may conceive that in such an animal, among the cells forming the *epiblast*, certain cells might become endowed with a

special sensitiveness to external changes, other cells being developed, like those of the hydra just mentioned, into special contractile structures. Thus the simplest form of a *reflex arc* (Fig. 127, B) might be formed. A further

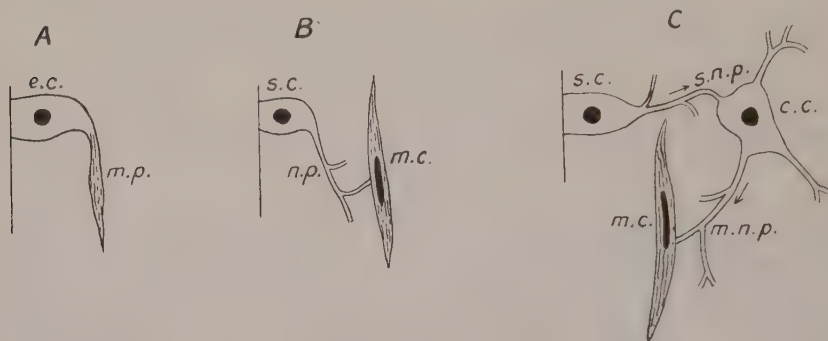


FIG. 127. Diagrammatic Representation of Evolution of a Nervous System.
(Modified from FOSTER.)

e.c., epithelial cell; *m.p.*, muscular process; *s.c.*, sensory cell; *n.p.*, nerve process or fibre; *m.c.*, muscle cell; *s.n.p.*, sensory nerve process; *m.n.p.*, motor nerve process; *c.c.*, central cell.

step in the development of such a hypothetical elementary nervous system would occur when certain "central cells" (Fig. 127, c) developed a special sensitiveness, not to mechanical changes in the environment, but to the protoplasmic excitatory process arriving at them from the sensory cells. This excitation they would pass to the muscle cell, *m.c.*, via the process, *m.n.p.*, and to numerous other muscle cells co-operating with *m.c.* via the other processes illustrated in the figure. But further, a network of such 'central cells' could be imagined forming a very primitive central nervous system.

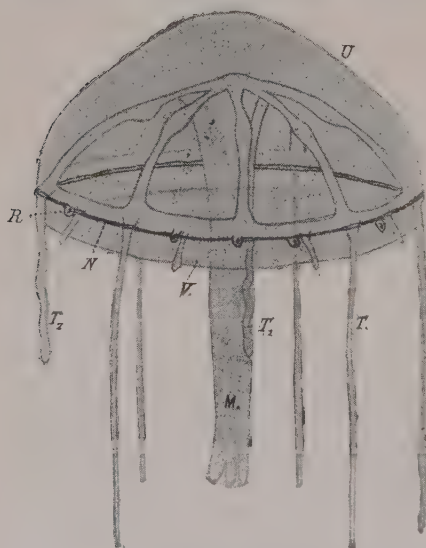


FIG. 128. Diagrammatic View of a Jelly-fish.
(HERTWIG.)

U, umbrella; *M*, manubrium; *T*₁, *T*₂, tentacles; *V*, velum; *N*, nerve ring; *R*, 'marginal body.'

confined to the under surface of the so-called umbrella with the tentacles and manubrium. A section through the umbrella shows a layer of epithelium containing differentiated sense cells, below which is a plexus, or rather network, of fine nerve fibres with a certain number of nerve cells at the nodes of the network. From this network fibres pass more deeply to end

A PRIMITIVE CENTRAL NERVOUS SYSTEM. In the lowest definite nervous system with which we are acquainted, that of the jelly-fish, all three types of cell, the sensory cell, the reactive or central cell and the motor cell, are already developed and have undergone among themselves a considerable degree of differentiation. In a jelly-fish or medusa, such as *aurelia* or *sarsia* (Fig. 128), the reactive tissue of the body is

in a finer network situated among a layer of muscle fibres formed, like the sensory cells, by a differentiation of the primitive epithelium or epiblast (Fig. 129). Besides this diffuse nervous system, there is a continuous ring of nerve fibres round the margin of the umbrella, thickened at intervals by the accumulation of nerve cells, which are in close relation to special

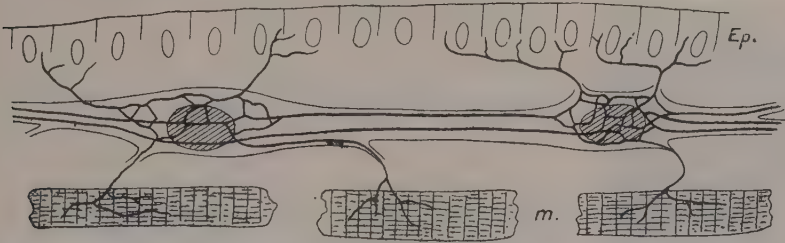


FIG. 129. Diagram of Subepithelial Plexus of Nerve Fibres and Nerve Cells, communicating on the one side with the sensory epithelium, and on the other side with the subumbrellar sheet of muscle fibres. (After BETHE.)

collections of sensory cells in the 'marginal bodies.' These sensory cells present a differentiation among themselves, some being apparently determined for the reception of mechanical stimuli, others for the reception of light stimuli, while others again are found in close relation with little masses of calcium carbonate crystals, by the direction of the weight of which the cells are able to react to changes in the position of the animal in space. In the jelly-fish, therefore, the nervous or reactive system has already acquired a considerable degree of differentiation.

A further differentiation of a nervous system, such as that just described, must in the first place involve the laying down of more 'long paths' and the

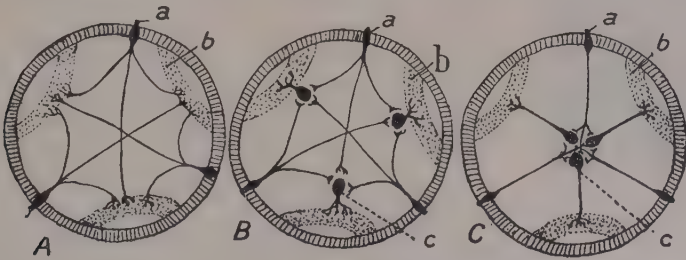


FIG. 130. Schema showing the Utility of the Multiplication of Neurons and their Grouping in Central Ganglia. (CAJAL.)

- A, an ideal invertebrate with only cutaneous 'sensory' neurones.
- B, invertebrate, such as a medusa, with sensory and motor neurones but no central nervous system.
- C, invertebrate (*e.g.* annelid) in which the motor neurones are concentrated in central ganglia.
- a, sensory neurone; b, muscle; c, motor neurone.

collection of the special 'central' cells into closely connected masses (ganglia), so as to concentrate the control of the reactions of the body, and to permit of the ready subordination of every part to the needs of the whole. (Cp. Fig. 130.) A special direction is given to this development by the evolution of animals, such as worms and crustaceans, which are segmented, one ganglion or pair of ganglia being provided for each segment.

DEVELOPMENT OF HEAD GANGLIA. In the act of locomotion it is of

advantage to the animal that those sense organs or sensory cells which are *projicient*, i.e. which are stimulated by changes in the environment originating at a distance from the animal, should be collected together near that part which goes first, the head end. Thus the projected sensations of sight, those which are excited by chemical changes in the surrounding medium and



FIG. 131. View of Central Nervous System of Crayfish. (After YUNG and VOGT.)

- a*, cerebral ganglion.
- b*, commissure.
- c*, subesophageal ganglion.
- g*, first abdominal ganglion.
- l*, oesophagus.
- m*, optic nerve.
- p*, antennary nerve.
- s*, stomato-gastric nerve.

represent the sense of smell, and those which are specially aroused by vibrations in the surrounding medium and correspond to those which we call the sense of sound, are in the majority of these animals subserved by organs situated near the head end. The wisdom of a man is measured by his foresight. The chances of an animal in the struggle for existence are determined by the degree to which the reactions of the animal to its *immediate* environment are held in check in response to stimuli arising from *approaching* events. An animal without power to see, smell, or hear its enemy will receive no impulse to flee until it is already within its enemy's jaws. It must therefore be of advantage to a segmented animal that the activities of the whole chain of segmented ganglia should be subservient to those central nerve cells which are in direct connection with the projicient sense organs at the head. The influence exerted by the head ganglia will in the first place be inhibitory of the direct reaction excited in each segment by stimulation of its surface; and, for this influence to be propagated, long tracks must be laid down, joining up ganglion to ganglion and propagating impulses from the head ganglia to the most distant part of the chain. As a type of such a system we may refer to the crayfish (Fig. 131), in which it consists of a chain of thirteen ganglia. In the abdomen and thorax the ganglia form a longitudinal series situated in the middle line. All give origin to a variable number of nerves which are distributed partly to the muscles, and partly to skin and sense organs. They are connected by longitudinal bands of nerve fibres. The most anterior of the thoracic ganglia is the largest. From this ganglion two commissures pass forward round the gullet behind the eyes, to unite in front of this tube with the transversely elongated mass of ganglion cells and fibres, called the supra-oesophageal ganglion. This consists of three fused pairs of ganglia. The most anterior gives origin to the optic nerves. From the middle ganglion on

each side a nerve passes to the integument, and from the inferior surface nerves pass to the internal antennæ. From these small branches are distributed to the organ of hearing. The posterior gives rise to the ganglion nerves which supply the large external antennæ of the animal. The first thoracic ganglion gives off ten pairs of nerves which are distributed to the mandibles, to the jaws or maxillæ, to the maxillipedes and to the branchial appendages of the latter.

THE PRIMITIVE REFLEX ARC. When we investigate the structural basis

of such a nervous system we find that, as in medusa, the starting-point of the reflex arc is in certain *neuro-epithelial* cells (Fig. 132) lying on the surface of the body. These cells are spindle-shaped; they have one short process passing to the surface, and a long process which runs in a nerve fibre, or collection of fibres, towards the ganglion of the segment. Arrived at the ganglion it divides into two branches, which travel to the two ends of the body and become lost in the granular material forming the inner part of each ganglion. The ganglia themselves consist internally of this 'punctate substance' or granular material, and externally of a capsule of ganglion cells. Each of the ganglion cells sends towards the centre one thick process which rapidly divides, some of the branches

passing into the granular material, while one branch runs outwards in a nerve to end in a network of fine fibrils within the muscle on the surface of the body. The nervous impulse excited in the sensory cell on the periphery travels therefore up a nerve fibre into the granular substance of the ganglion. From this granular substance it is collected by the fine branches of the ganglion cells and is transmitted by them along the motor nerve fibres to the muscles. The central granular material consists entirely of a close feltwork of fibres which may be regarded as processes either of the sensory nerve fibres or of the nerve cells. The typical reflex arc in this case, therefore, is formed by two nerve cells with their processes. Such a nerve cell with its processes is spoken of as a *neuron*. The first neuron, the recipient neuron, or *receptor*, is represented by the sensory cell with its two processes in the granular material. The second neuron is formed by the ganglion cell with its finely branched dendritic processes in the granular matter and its motor axon which passes into the muscle fibres.

THE EMBRYOLOGY OF THE CENTRAL NERVOUS SYSTEM.

In vertebrates, as in the invertebrata, the central nervous system is developed by an involution of the epiblast, revealing thus its primitive relations to the surface of the body. At an early period in foetal life, shortly after the formation of the two layers of epiblast and hypoblast, a thickening is observed in the epiblast. This thickening soon forms the neural groove (Fig. 133), and this in turn folds to form the neural canal, which is dilated at the head end of the embryo to form three enlargements known as the cerebral vesicles.

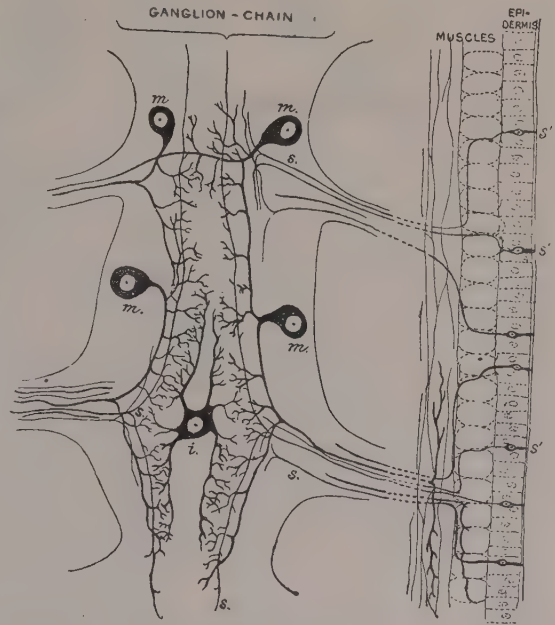


FIG. 132. Diagram of Nervous System of a Segmented Invertebrate (Earthworm or Crayfish). (From SCHAFER, after RERZIUS.)

s', sensory cells; *s*, afferent nerve fibres; *m*, motor neurone; *i*, central or intermediate cell.

When first formed the canal is oval in cross section, its wall being made up of a layer of columnar cells, which eventually form the supporting tissue of the adult central nervous tissue, known as the *neuroglia*. These cells, formed

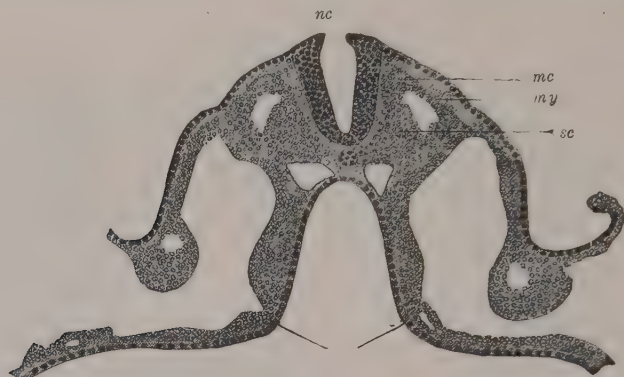


FIG. 133. Transverse section of Human Embryo of 2.4 mm. to show developing Neural Canal. (T. H. BRYCE.)

nc, neural canal; *mc*, muscle plate; *my*, outer wall of somite; *sc*, sclerotome.

from the most superficial layer of the invaginated epiblast, are spoken of as *spongioblasts*. The deeper layer of cells, known as *neuroblasts*, rapidly divide and form a thick layer surrounding the internal layer of spongioblasts, through which pass the peripheral processes of the latter. When first formed

these cells have no processes. Later on each neuroblast acquires a pear shape, the stalk of the pear having a somewhat bulbous extremity (Fig. 134). The stalk continually elongates, and the elongated process may leave the spinal cord altogether and grow outwards to any part of the body of the embryo, or may pass to other parts of the central nervous system. This long process of the developing nerve cell is known as the *axon*. Some time after its formation other processes grow out from the cell, which soon branch and end in the immediate neighbourhood of the cell. The axons of the cells near the ventral part of the neural tube grow out to the different muscles of the body, where they end in close connection with the muscular fibres by an arborisation which forms the end plate. They provide a motor path for impulses running from the central nervous system to the musculature of the



FIG. 134. Neuroblasts from the Spinal Cord of a Chick Embryo. (CAJAL.)

A, three neuroblasts stained to show neurofibrils; *a*, a bi-polar cell. B, a neuroblast showing the 'incremental cone' *c*.

body. The sensory path, *e.g.*, from skin to central nervous system, is formed in a somewhat different manner. Even before the neural groove has closed in, a thickening of the epiblast is seen immediately external to the groove on each side. This thickening becomes divided into a series of collections of cells lying immediately under the epiblast on the

lateral and dorsal surface of the neural canal. The cells, which are at first round or oval, send off two processes in opposite directions so that they become bipolar (Fig. 135). One process passes into the central nervous system where it divides, some of its branches being distributed in the nervous system at the same level, while others run a considerable distance towards the head immediately outside the tube of nerve cells. The other process grows downwards, along with the processes from the ventral cells of the tube, towards the periphery of the body, where it ends in close connection with the surface in the various sense organs of the skin and muscles. These collections of bipolar cells form the posterior root ganglia. In fishes they

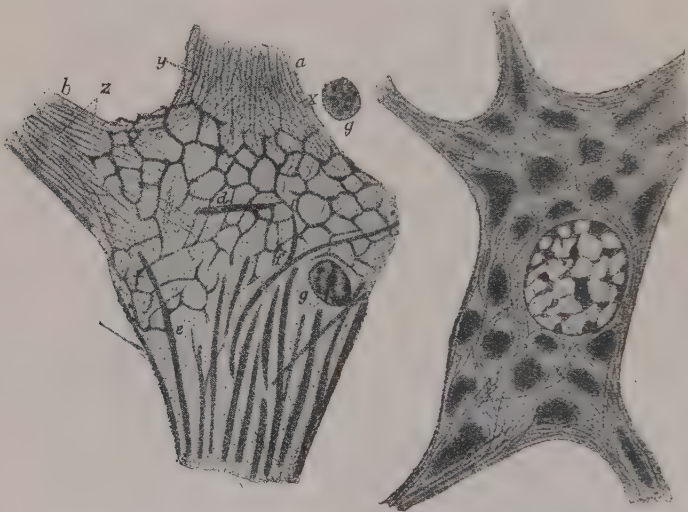


FIG. 135. Section through developing Spinal Cord and Nerve Roots from Chick Embryo of fifth day. (CAJAL.)

A, ventral root; B, dorsal root; C, motor nerve cells; D, sympathetic ganglion cells; E, spinal ganglion cells still bipolar; F, mixed nerve; *b*, *c*, *d*, motor nerve fibres to *f*, developing spinal muscles; *e*, a sensory nerve trunk.

retain their primitive character throughout life, but in mammals the bipolar cell is to be found only in the spiral and vestibular ganglia, which give origin to the fibres of the eighth nerve. In all the other ganglia the shape of the cell becomes modified by an approximation of the points of attachment of the two processes until finally the cell becomes unipolar, with one process which divides by a T-shaped junction into two, one running towards the spinal cord, while the other takes a peripheral course as the afferent nerve fibre. The central nervous system thus becomes provided with a 'way in' and a 'way out' for the chain of impulses concerned in a nervous reaction or reflex action. The further development of the spinal cord is mainly determined by the extension of the axons of the cells outside the tube, and by the provision of the 'long paths' which are a necessary condition of increased

efficiency of the reacting organ. Some time after the outgrowth of the axon a medullary sheath is formed, apparently by the agency of the axon itself, so that each group of axons leaving or entering the cord forms a bundle of medullated nerve fibres. The long branches of the posterior or dorsal roots running up towards the head form a mass of fibres behind the tube of cells known as the posterior columns. Fibres starting in the spinal cord itself run upwards and downwards to end in other parts of the cord, or in the more anterior divisions of the central nervous system forming the brain; and they surround the neural tube on its ventral and lateral aspects with a sheath of white matter. To these white fibres are added others, which take origin in the brain and pass all the way down the cord. Meanwhile the cells themselves become separated by the ramifications between them of the branches of axons entering the cord, as well as of the dendrites of the cells themselves. Thus in its adult form, the spinal cord consists of a central



FIGS. 136 and 137. Nerve Cells from Spinal Cord. (BETHE.)

Fig. 136, showing Golgi Network, and Neurofibrils: *d, e, f*, junctions of axons with Golgi network.

Fig. 137, showing Neurofibrils and Nissl Bodies.

mass of nerve cells and fibres, known as the *grey matter*, which is encased in a sheath of white matter formed of medullated nerve fibres. The cord itself is cylindrical in shape, and is divided into two symmetrical halves by the anterior and posterior fissures. In each half of the cord the grey matter on cross section is crescentic in shape, presenting an anterior or ventral horn and a posterior or dorsal horn; it is connected with the corresponding mass in the other half of the cord by grey matter known as the anterior and posterior grey commissures. Between the two grey commissures is the central canal, relatively very minute when compared with the condition in the foetus and lined by a single layer of ciliated columnar epithelium, the cells of which are directly descended from the neural epithelium lining the medullary canal.

THE STRUCTURE OF NERVE CELLS. In the adult animal a typical nerve cell is a large cell with many branches. It has a large vesicular nucleus with very little chromatin, which may be collected around the nucleoli. When treated fresh with methylene blue, or hardened by alcohol

or corrosive sublimate and stained with methylene blue or toluidine blue, the protoplasm is seen to contain angular masses which are deeply coloured with the dye (Fig. 137). These masses are known as the *Nissl granules*. By other methods it is possible to demonstrate that the whole protoplasm of the cell between the Nissl bodies is pervaded by fine fibrils, which enter the cell from the processes and may run out of the cell by the axon or may pass into some of the other shorter processes (Fig. 137). The processes of the cell, as shown by their development, are of two kinds. The axon, which becomes continuous with the axis cylinder of the medullated nerve fibre, and the dendrites, which may be very numerous. They rapidly diminish in size as they give off branches, which apparently terminate freely in the grey matter in the immediate neighbourhood of the cell. In specimens stained by the Golgi method the dendrites may sometimes present a serrated outline. The Nissl bodies of the cell extend some way into the dendrites. A nerve cell with all its processes, axon and dendrites is spoken of as a *neurone*. From the development of the central nervous system in vertebrates, we see that the nervous path of every reaction must be made up of two or more neurones. If we take, for example, the simplest possible reaction which might be effected through a single segment of the spinal cord, the afferent impulse might be started by some stimulus applied to the ramifications in the skin of the distal processes of the posterior root ganglion cell (*cf.* Fig. 135). The nerve impulse so started is carried by the nerve fibre past the T-shaped junction in the posterior root ganglion into the cord, and along a branch of the entering nerve fibre which runs right across the cord to terminate in the neighbourhood of the anterior horn cells. Here the impulse must be transmitted in some way to the dendrites or body of one of the large motor nerve cells in the anterior horn, whence it is carried along the axon of the cell, leaving the cord by the anterior root and passing down a peripheral nerve to the end plate on a muscle fibre. Here again by some means the arrival of the impulse excites the muscle to contract.

ONE-WAY CONDUCTION

This transmission never takes place in the contrary sense, *i.e.* no impulse started in the motor nerve can travel back through the spinal cord and along the sensory nerve. Although an impulse excited in the nerve passes easily to the muscle, an excitatory process started in the muscle itself is confined to this tissue and never extends to the nerve fibre. Apparently the same rule holds good within the grey matter of the central nervous system, where two neurones come into relation with one another. An impulse passes easily from the axon of one into the dendrites and cell of another neurone but, so far as we are aware, it is impossible by exciting an axon to cause a retrograde wave of excitation to traverse its corresponding cell into the terminations of the axons in immediate contact with the cell. This statement has been called by Sherrington the 'Law of Forward Direction.' The character of a reaction to any stimulus, applied to the surface of the body, is determined by the course which the impulse, excited in the afferent nerves, takes on entrance into the central nervous system. This course is laid down by the connections of the neurones through which the nerve impulse passes. In the central nervous system therefore, more than in any other part of the body, function is directly dependent on structure. Theoretically if we had a perfect knowledge of the connections of the neurones in the central nervous system as well as of the nerve fibres affected by any given stimulus, we should be able to prophesy exactly the result of such stimulus. In the

case of the simpler reactions this is already possible, but in the higher parts of the nervous system the enormous complexity of the systems of neurones excludes any possibility of our forming more than a general idea as to the nerve paths traversed in any given reaction; and the variations which exist from individual to individual must in the intact animal always prevent an absolute prediction of the results of any stimulus.

GENERAL CHARACTERISTICS OF REFLEX ACTIONS

There are certain features common to all responses, carried out by the medium of the central nervous system, which must be regarded as determined by the properties of the neurones, *i.e.* the conducting links in the chain of excitatory tissues intervening between the stimulated spot on the exterior and the reacting tissue, muscle or gland. These characteristics may be roughly classified as follows:

(1) **LOCALISATION.** In a simple system of neurones a given stimulus will nearly always produce the same reaction. In a frog possessing only a spinal cord, the upper parts of the central nervous system having been destroyed, any harmful stimulus applied to a toe will cause a lifting of the leg. If the motor nerve to the *gastrocnemius* be excited, the whole muscle contracts. If one of the nerve roots entering into the formation of the sciatic nerve be excited, only certain fibres of the *gastrocnemius* contract, the locality of the reacting fibres being determined by their connection with the excited nerve fibres. In the same way the contraction of certain muscles of the leg, in response to a stimulus applied to the skin of the foot, is determined by the fact that the nerve fibres, which carry the impulses from the toe into the spinal cord, divide there and make connections with the motor neurones, whose axons are distributed to the several muscles involved in the reaction. The connection of the sensory with the motor neurone may be direct, but in most cases the impulse has to pass through intermediate neurones before arriving at the motor neurones. The path of the impulse however, in spite of its enormous extension, is as definite as is the path from an excited motor nerve root to a muscle fibre.

(2) **DELAY.** Instead of one nerve-ending intervening between the stimulated nerve and the reacting tissue, there may be, in the case of the reflex action, two, three or more nerve-endings interpolated in the path of the impulse. These nerve endings are the fields of conjunction, the *synapses*, between the axon of one neurone and the dendrites and cell body of the neurone next in the chain.

We have seen that there is a distinct difference between the latent period of a muscle excited through its nerve as compared with the latent period when excited directly; and we ascribed this latent period to a delay in the motor end plate. We should expect therefore to find that the delay or latent period in the case of a reflex action, *i.e.* the time lost in the conversion of an afferent into an efferent impulse in the central nervous system, would be appreciable and would increase with the complexity of the response—that is, with the number of neurones involved in the reaction. Such is indeed the case.

In determining the actual 'lost time' in the central nervous system for any given reflex, it is necessary to subtract from the total delay, interposed between the application of the stimulus and the resultant movement, the time taken by the impulse in travelling to and from the central nervous system, as well as the latent period of the muscles themselves. The remainder is known as the 'reduced reflex time.' Wundt found in the frog, when a reflex contraction of the *gastrocnemius* was excited by a stimulation

of a posterior root of the same side, that the reduced reflex time was 0.008 sec. For a crossed reflex the delay was increased by 0.004 sec. If we assume that one additional neurone is involved in the crossed reflex, the lost time at a synapse would be 0.004 sec.; if two cells are intercalated, the synapse delay would be only 0.002 sec. Since the uncrossed reflex has a delay of 0.008 sec., at least two synapses are involved in the path of this simple reflex.

The blinking excited by stimulation of the eyelid has a reduced reflex time of 0.047 sec.

(3) **SUMMATION.** When contractile tissues, such as striated or unstriated muscle, are excited by single shocks, a certain minimal strength of stimulus is necessary in order to produce a contraction. Weaker stimuli are spoken of as subminimal, and when applied singly have apparently no effect on the muscle. In dealing with the properties of involuntary muscle, we saw that a subminimal stimulus is not necessarily devoid of effect because it fails to evoke a contraction, since, if repeated at sufficiently frequent intervals, a *summation* of stimuli occurs. Thus at the fifth or sixth application a stimulus which was previously ineffective becomes effective and a contraction results. The muscle will now continue to respond to each stimulus, but, if the excitations be discontinued for a time, reapplication of a stimulus of the same strength becomes once more ineffective. This summation of stimuli is a prominent feature in all reflex actions, so much so that it may be often impossible to evoke a reaction to a very strong single induction shock, whereas the application of a tetanising current too weak to be felt on the tongue may produce a marked reaction. We shall have occasion later on to deal with special examples of this summation of stimuli.

(4) **FATIGUE.** In the nerve-muscle preparation the weakest point and that which soonest suffers from fatigue is the end plate, or rather the field of conjunction of nerve fibre and muscle fibre. In the central nervous system the synapses of the different neurones are equally susceptible, and since several of such synapses are involved in every reflex action, we should expect to find that the central nervous system would show signs of fatigue before the peripheral structures. If a given reaction be repeatedly elicited by applying a stimulus to a certain area of the surface, the reaction becomes feebler and finally disappears altogether, long before any signs of fatigue in the motor apparatus can be detected on stimulation of the motor nerve itself. The fatigue ensues equally if the reaction be excited by stimulating a sensory nerve directly, and since we know that it is practically impossible to fatigue nerve fibres, we must conclude that the seat of fatigue is in the grey matter of the spinal cord itself.

(5) **'BLOCK' OR RESISTANCE.** In the central nervous system there is an absolute block to the passage of an impulse backwards through a synapse, *i.e.* from a nerve cell or its dendrites into the end ramifications of an axon. The phenomena of fatigue show that at the synapse there is a certain degree of resistance to the passage of an impulse in the normal direction, and that this resistance is rapidly increased under the conditions which produce fatigue. When we study the structure of the central nervous system more fully, we find that although there are certain shortest possible paths, *i.e.* ones involving few neurones, for every impulse arriving at the central nervous system, yet so extensive is the branching of the entering nerve fibres and so complex are the neurone systems with which they come in connection that an impulse entering along one given fibre could spread to practically every neurone in the spinal cord and brain. Such a result is indeed observed in animals poisoned by strychnine. In such animals the

slightest stimulus applied to any part of the skin excites strong tonic spasms in the whole musculature of the body. Every sensory nerve fibre, that is to say, can discharge into every motor neurone of the cord. That this result does not ensue on localised stimulation in a normal animal is dependent on the varying resistance to the passage of an impulse into the several neurones with which the entrant fibre comes in relation. A small stimulus will discharge only along the few neurones where the resistance is lowest. Increase of the stimulus, either by adding to its strength or by summation of weak stimuli, will enable the impulse to spread along more neurones, and therefore will elicit a more widespread response. Only when the 'blocks' are entirely removed by the administration of strychnine, or when the stimuli are abnormally powerful and long continued, will the impulse spread to all regions of the central nervous system, so that the response becomes general and inco-ordinate instead of local and adapted to the stimulus.

(6) **FACILITATION OR 'BAHNUNG.'** The passage of a nervous impulse across a synapse or series of synapses in the central nervous system has a twofold effect. If the passage be too often repeated, phenomena of fatigue are produced and there is an increase of the block at each synapse. If however the stimulus be not excessive and the reaction not too frequently evoked, the effect of the passage of an impulse is to diminish the resistance, so that a second application of the stimulus elicits the reaction more easily. The process of summation in fact is chiefly in the direction of removal of a block. We have a close analogy to this process of facilitation in the 'staircase phenomenon' observed in cardiac and unstriated muscle. In these tissues the repetition of a subminimal stimulus in time renders it effective, and then repetition of the now effective stimulus causes a gradually increasing height of contraction, which depends on the state of the contracting tissue itself and cannot be brought about by changes in the strength of the stimulus. This process of facilitation or 'Bahnung' is of great interest in connection with the development of 'long paths' in the central nervous system, and more especially with the acquirement of new reactions by the higher animals. The Law of Facilitation is really the Law of Habit. When an impulse has passed once through a certain set of neurones to the exclusion of others, it will tend, other things being equal, to take the same course on a future occasion, and each time that it traverses this path the resistances in the path will be smaller. Education is the laying down of nerve channels in the central nervous system, while still plastic, by this process of 'facilitation' along fit paths, combined with inhibition (by pain) in the other unfit paths. Memory itself has the process of facilitation as its neural basis.

(7) **INHIBITION.** The constant occurrence of a reaction in response to a given stimulus is obtained only if care be taken to isolate the segment of the central nervous system involved from the entry of other afferent stimuli. As a rule, if two stimuli be applied simultaneously at different points, the reaction which ensues will not be a combined one—the resultant of the reactions which would be normally conditioned by each single stimulus, but will be a response to one of the stimuli, which we must therefore regard as the more effective. The reaction to the other stimulus is either abolished altogether or comes on after a considerable period of delay. The central nervous system can apparently attend only to one thing at a time. In physiological terms we should say that every effective reaction inhibits every other reaction. In the spinal cord of the frog the normal withdrawal of the foot in response to stimulation of the toe of the same side can be inhibited by strong stimulation of the other sciatic nerve, by stimulation of the spinal cord at a higher level or by stimulation of the optic lobes.

Immediately after pithing the brain of the frog, the whole animal becomes flaccid and motionless, and for the next few minutes it is impossible to elicit any reaction by stimulation, however strong, applied to the skin of the body. In the production of this condition of 'shock' the inhibition of all the spinal centres, produced by the strong stimulation of the injury to the brain and medulla, plays at any rate an important part. We may say that the passage of an impulse through a chain of neurones diminishes the block for subsequent impulses at each synapse that it traverses, but increases during its passage the block in all the adjacent synapses.

In dealing with the special reactions of the spinal cord, we shall have occasion to refer more fully and in greater detail to many of these properties which are characteristic of all reflexes. Before treating of the functions of the separate parts of the central nervous system in the higher mammals, it may be of interest to consider the exact nature of the structure intervening between neurone and neurone at each field of conjunction or synapse, as well as the significance of the two chief elements of the central nervous system, *nerve cell* and *nerve fibre*, in the production of co-ordinated purposive reactions.

THE INTIMATE NATURE OF CENTRAL SUMMATION AND INHIBITION. When we examine the structure of the central nervous system we find nothing but a complicated series of arcs and nerve fibres with their cells, in which each member makes contact with the next by a synapse resembling in many features the motor nerve-ending intervening between nerve and muscle. We ought therefore to be able to find some analogy between summation and inhibition in the central nervous system and corresponding phenomena in the nerve-muscle preparation. Keith Lucas and Adrian have shown that these phenomena are not peculiar to the central nervous system. When dealing with the physiology of nerve fibres, we have seen that after a short refractory period the excitability of nerve to an external stimulus, or to the physiological stimulus provided by a neighbouring segment, returns gradually to normal, so that if a nervous impulse follow a predecessor too closely, it is diminished in amount and resembles one which is passing through a region where the excitability has been diminished by a narcotic. This subnormal phase of conductivity and excitability is succeeded by a supernormal phase of recovery (Fig. 138). Those impulses, which are repeated at such an interval that each falls in the supernormal phase of recovery left by its predecessor, are more readily conducted through such a region than is an impulse of normal intensity. A series of impulses properly timed may therefore pass when a single impulse will fail. We have every reason to believe that junctional tissues such as the motor end-plate and the synapses in the central nervous system represent regions such as can be produced artificially in the course of a nerve fibre by narcotisation. The summation which we have seen to occur in the central nervous system may be therefore of the same nature as the summation which can be observed in a narcotised nerve fibre.

But the reverse also holds good. If each stimulus or impulse falls in the phase of subnormal irritability which immediately succeeds the refractory phase, it will fail to pass whereas the first impulse will pass. Thus if a motor nerve be stimulated with rapidly repeated induction shocks for several minutes, the contraction of the muscle dies down. Stimulation is then stopped for a few seconds; when started again, the muscle responds with a single twitch only. Now it is observed that so long as the rapid stimuli are continued, no contraction is evoked by single stimuli applied to the nerve at a point nearer the muscle. The rapid stimulation above inhibits the effect of

the single stimulus near the muscle. In some way or other there has been produced a failure of conduction in the motor nerve ending. In this case the rapid stimuli are falling in the subnormal phase of conductivity of the region of diminished excitability; since they succeed one another rapidly, this region remains in a condition of subnormal conductivity so that any single stimulus is unable to pass.

We may imagine a somewhat similar mechanism for the inhibition which is a constant accompaniment of any reflex action. Thus if the foot of a spinal dog be pricked, the flexors of the leg and thigh contract, while the extensors are inhibited. This condition is known as *reciprocal innervation*. In the diagram (Fig. 139) we may imagine that A represents the flexor and B the extensor: $x_1, x_2, x_3, y_1, y_2, y_3$ are synaptic areas of diminished excitability. If we suppose the tract x_1, x_2 to have a longer refractory period than x and y , the latter conducting easily 100 impulses per second, while x_1, x_2 can conduct only 50 impulses per second, every other impulse from x , the sensory nerve, will fail to pass x_1, x_2 . Stimulation at x will therefore send 50

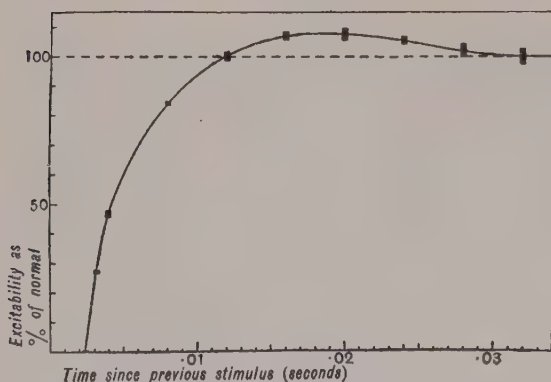


FIG. 138. Graph of Changes in the Excitability of a Nerve which result from a single Maximal Stimulus. (KEITH LUCAS.)

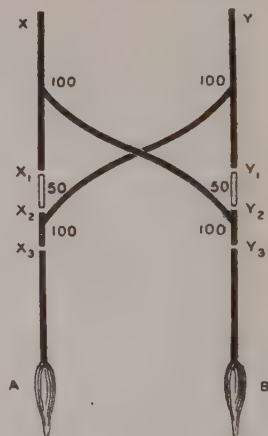


FIG. 139.

impulses per second to A, and will cause it to contract. We may imagine that B is kept in a constant tonic contraction by a series of impulses of low intensity arriving at y at the rate of 50 per second. When x is stimulated, however, 100 impulses per second will arrive at y_2, y_3 . This will act like the tetanising current in the experiment on the nerve muscle preparation just quoted. y_3 may be supposed to be of such a nature that, whereas 50 impulses per second will fall in the phase of supernormal recovery, 100 will fall in the subnormal phase, and therefore will fail to pass. The effect of stimulation at x will thus be to cause contraction at A and complete cutting off of all possible impulses from B, thus giving us the reciprocal innervation, producing contraction of one set of muscles and inhibition of its antagonists. The other nerve y will have the same action on A that x has on B.

NATURE OF THE CONNECTION BETWEEN NEURONES.

The study of the development of the central nervous system in higher animals has shown that this system is made up of neurones, the connections of which determine the possible paths of impulses in the adult cord. In the nerve-muscle preparation there is an apparent break of structure at the termination of the nerve in the muscle fibre, any continuity between nerve-ending and contractile substance being subserved by

undifferentiated protoplasm. There is thus no difficulty in conceiving a propagation across a similar nerve-ending or synapse, between the axon of one neurone and the cell body or dendrites of another neurone. If, however, the conception we have formed above of the evolution of a nervous system from a continuous conducting protoplasmic network, by a process of 'facilitation' attended by histological differentiation, be correct, we should expect to find in the fully developed brain and spinal cord some traces at any rate of continuity throughout the whole system of neurones. The question as to the existence of anatomical continuity from neurone to neurone has been hotly discussed both for vertebrates and invertebrates. In the case of the latter, evidence in favour of the continuity of neuro-fibrillæ from sensory surface to reacting tissue is very strong. Many

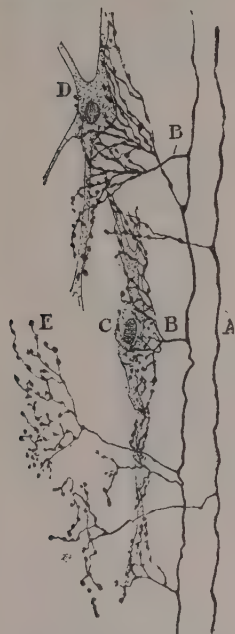


FIG. 140. Arborisation of Collaterals from the Posterior Root Fibres round the Cells of the Posterior Horn. (RAMÓN Y CAJAL.)

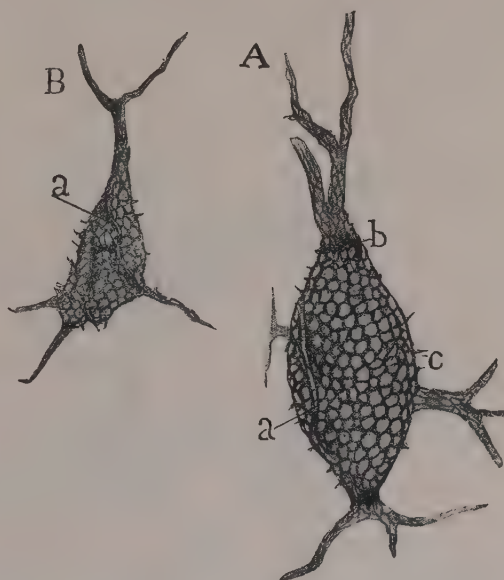


FIG. 141. Superficial Network of Golgi surrounding two Cells from the Cerebral Cortex of the Cat. Ehrlich's method. (CAJAL.)

A, large cell, B, small cell, *a*, folds in the network; *b*, a ring-like condensation of the network at the poles of the larger cell; *c*, spinous projections from the surface.

observers have described a similar continuity in the nervous system of mammals. It is easy to show the existence of a fibrillar structure both in the nerve cell and in the nerve fibre. The axis cylinder of the nerve fibre can be regarded as made up of fine fibrillæ embedded in an interfibrillar substance. At the nodes of Ranvier the interfibrillar substance is interrupted, the fibrillæ alone extending into the next internode and representing the continuous structure which determines the conducting power of the nerve fibre. In the nerve cell the fibrillæ occupy all the space between the Nissl bodies, passing from dendrite to dendrite, and many of them from all the dendrites and all parts of the cell sweeping through the axon hillock to form the fibrillæ of the nerve fibre. The existence of these fibrillar structures in nerve cell and nerve fibre is accepted by most histologists. The question however of the connection between the fibrillæ of one axon and those of the next neurone, *i.e.* the histology of the synapse, presents much greater difficulties and has excited

much difference of opinion. If we examine a nerve cell such as a cell of Purkinje of the cerebellum, or a cell of Clarke's column in the cord, we find that it is surrounded by a thick basketwork of fibres which are the arborisations or end terminations of the axons which pass to the cell to enter into functional relationships with it (Fig. 140). This pericellular network is of great extent and may equal in total diameter the diameter of the cell itself. Whether the basketwork is really a network, or merely a feltwork in which the fine fibres intertwine among each other without becoming actually continuous at any point, is difficult to make out. On the periphery of the cell itself another network has been described and is known as the Golgi network (Fig. 141). This has been displayed by the process of impregnation with silver chromate (Golgi method), as well as by staining with methylene blue. Some authors have regarded this network as an artefact due to precipitation of albuminous fluids on the surface of the cell. According to Bethe, however, the Golgi network on the one hand receives fibres from the

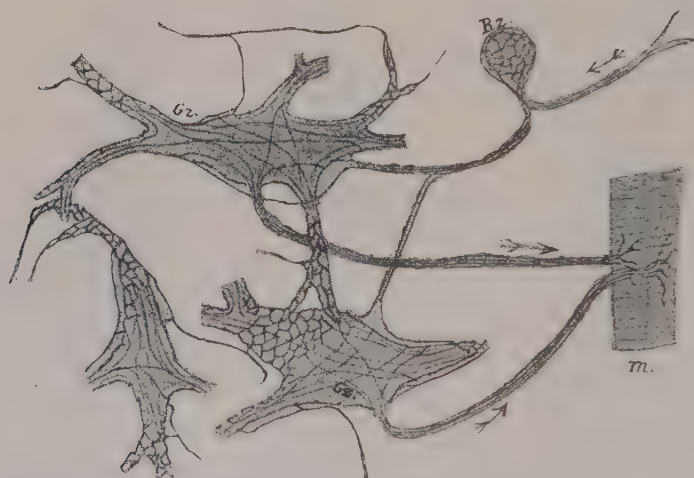


FIG. 142. Schema of the Neurofibrillar Continuum, involved in an ordinary Reflex Act, in a Vertebrate Nervous System. (BETHE.)

encircling pericellular basketwork of axons, and on the other hand gives off towards the interior of the cell fine fibrils, which are continuous with the neurofibrillæ of the cell and pass out in its axon. The diagrammatic course of a nerve impulse according to Bethe is represented in the accompanying diagram (Fig. 142). An impulse starting from the periphery of the body travels up the distal process of the posterior root ganglion cell, passes either through the cell or directly to the central process, and runs along this to the terminations of the posterior root fibres round a posterior horn cell. Here it passes into the pericellular basketwork or axon network, thence into the Golgi network and along the fibrillæ of the cell, out by the fibrillæ of the axon and so to a fresh synapse with a cell of the anterior horn.

There are certain physiological difficulties in the acceptance of this doctrine of continuity through the central nervous system. Thus in the central nervous system injury to one axon causes degeneration of the axon below the point of section, but the degeneration stops short at the end arborisation and does not spread into the next neurone. We may assume that, in consequence of the fineness of the branchings, the propagation through the synapse

is especially difficult. Thus, many of the phenomena, described above as characteristic of the reactions which take place in the central nervous system, would easily be explained on the theory of continuity of the fibrillæ. The serious difficulty in the acceptance of this theory is however the 'Law of Forward Direction,' i.e. the fact that an impulse will pass from an axon to the next neurone, but will not pass backwards across the synapse from the cell body to the contiguous axon.

It is possible that we may have to distinguish two types of nervous systems, viz. : (a) A neurofibrillar type, specially developed in invertebrata, with conduction in all directions ; and (b) A synaptic type, in which the Law of Forward Direction holds, of later evolution and forming the greater part of the nervous system of vertebrata.

FUNCTIONS OF THE NERVE CELL. When an unicellular organism containing a single nucleus is cut into two parts, both continue to live for some time, each performing active movements and evincing all the phenomena which we associate with activity and, therefore, with destructive catabolism. For the continued existence of a cell the processes of constructive metabolism or anabolism must take place *pari passu* with those of disintegration, and for this the presence of the nucleus is necessary. Hence, in a few days, the half cell with the nucleus has repaired its loss and become once again a normal individual, whereas the half without a nucleus undergoes degeneration and death. The axon of a nerve cell can be regarded as analogous to a long pseudopodium of an amœba. Like this, if cut away from that part of the cell containing the nucleus, though capable for a time of discharging its active function of propagation of excitatory impulses, it finally dies, death of the nerve fibre occurring in the mammal within three to five days after separation of the axon from the cell. Every nerve cell, therefore, may be looked upon as the trophic centre of the nerve fibre proceeding from it, as well as of the medullary sheath which is practically a product or secretion of the axis cylinder.

But has the nerve cell any more important functions to discharge ? It has long been customary to endow the nerve cell with all the properties which are distinctive of a nervous system, and to ascribe to it the active part in the origination of automatic actions, in the reflection of afferent impulses and in the supply of energy to all nervous processes. That the passage of impulses through the nerve centres requires the expenditure of energy by these centres can be proved in various ways. In the first place, there is the fact that in all nervous systems, at any rate of the higher animals, arrangements are made for their free supply with oxygen. Very short deprivation of oxygen causes a complete block throughout the system, in many cases preceded by a short period of increased excitability or ease of transmission. If, in the rabbit, the thoracic aorta be clamped for a few minutes, the hind limbs become paralysed ; and if the obstruction be continued for half an hour, there is widespread degeneration and death of the cells with their fibres in the grey matter of the lumbar and sacral cord. In the second place, the ready production of fatigue of the nervous system points to a considerable using up of material as a condition of the passage of nerve impulses. In many instances, moreover, an infinitesimal stimulus travelling up a few nerve fibres may excite widespread activity of the whole central nervous system with the discharge of impulses along practically every nerve of the body. Thus the presence of a crumb on the larynx will excite impulses passing up the superior laryngeal nerve, which in themselves can involve but little expenditure of energy. The result, however, of their arrival at the central nervous system is the discharge of impulses along the motor

nerves causing spasmodic contractions of almost every muscle in the body.

It seems beyond doubt that energy is evolved in the central nervous system as a result of metabolic changes, and that energy may be added to impulses passing through the central nervous system, which therefore acts as a relay of force. But this activity does not necessarily require the presence or co-operation of nucleated cells. In dealing with the nature of a nerve impulse, we had reason to conclude that there may be an actual, though minimal, liberation of energy in the axis cylinder with the passage of each nerve impulse. The non-nucleated parts of a cell, whether the axon or the cell body, are equally capable of this evolution of energy, and we might conceive therefore of a nervous system which, existing for a few days, might act as a normal reflex centre in the entire absence of the nucleated cell bodies.



FIG. 143. Diagrammatic Representation of the Brain of *Carcinus* to show the Parts involved in Bethe's Experiment.

The dotted line *x* shows the incision employed to isolate the neuropile of the ganglion of the second tentacle.

This conception has been realised by Bethe in an experiment on the crab (*Carcinus menas*). In this animal the reflex movements of the tentacle are carried out by a ganglion situated at its base. As in the other Crustacea, the cell bodies in this ganglion lie outside the mass of neurofibrils in the centre, forming a sort of capsule (Fig. 143). Bethe was able, under the dissecting microscope, to remove the cell bodies without interfering with the nerves entering or leaving the central mass of fibrils. All the nerve processes with their connections were therefore left intact. In animals operated on in this way, Bethe found that for two or three days the tentacle reacted normally to stimuli applied to its surface. The reflex functions of the ganglion were not in any way affected by the removal of the nucleated bodies of the cells. A similar experiment would be impossible in the central nervous system of vertebrates, since impulses must of necessity pass through the cell body on their way from the termination of one axon to the beginning of the next. In the spinal root ganglion, however, most of the cells lie on the surface. In the rabbit Steinach exposed a posterior root ganglion, separating it from all

its vascular supply but leaving its nervous attachments intact. The wound was opened every day for the next few days and an instrument passed under the ganglion so as to divide any newly forming vessels. As a result of the deprivation of blood supply the ganglion cells died. But Steinach found that nerve impulses were still conducted perfectly well through the ganglion at a time when microscopic examination showed a complete atrophy of all cells. It is therefore only in virtue of the fact that the nerve cell is the seat of the nucleus, and therefore of the assimilative functions of the neurone, that any pre-eminent importance can be ascribed to it in the building up of a reactive nervous system.

AUTOMATICITY. Prominent among the functions with which the nerve cell has been endowed is that of *automaticity of action* in the absence of stimulus other than that supplied by its own metabolism or by the fluids which bathe it. *A priori* there is no reason to deny to the neurone a property which is possessed by other cells of the body, such as the muscular cells of the heart, and is a fundamental quality of undifferentiated protoplasm. The purpose, however, for which these cells have been evolved and differentiated is that of reaction, of adapting the organism to changes in its environment; and it is doubtful whether, in this differentiation, it has retained any automatic properties whatsoever. In the absence of any afferent impulse the whole central nervous system would probably be inert. In a frog retaining only the spinal cord Hering divided all the posterior roots. The frog remained flaccid and motionless. Injection of strychnine was powerless to evoke the usual tetanic spasms. In such a strychninised frog, however, it was necessary only to open the wound and touch one of the divided posterior roots to throw the whole body into convulsions. As shown by Sherrington and Mott, division of all the afferent nerves coming from the upper limb in monkey or man entirely abolishes all such contractions of the limb as are usually effected through the intermediation of the cerebral cortex. Cutting off the major portion of the afferent impulses to the respiratory centre does not, it is true, abolish all respiratory discharges, but converts the rhythmic respirations into a series of inspiratory spasms which are repeated at long intervals and are entirely inadequate for the proper aeration of the blood. According to Sherrington, a repetition on the mammal of Hering's experiment does not lead to the same results, since a spasmodic discharge is produced from the isolated spinal cord as a result of asphyxia. But it is doubtful whether in this case there was not some continuous excitation of the cord going on, as a result of the closure of the demarcation current in the cut ends of the posterior roots by the body fluids. It is possible that the neurones possess some automatic power, *i.e.* some power of initiating nervous processes, as a result of changes in the fluids surrounding them. This automaticity, however, is not a prominent feature of the nervous system, which has been evolved as a purely reactive mechanism to the afferent impulses resulting from the material changes which are continually taking place in the environment of the animal.

DEGENERATION OF NERVE. When an axis cylinder is severed histological changes are found to occur in both the cell and the axis cylinder. The cell suffers *chromatolysis*, and shows the following changes:—(a) swelling of the cell bodies, which lose their polygonal shape and become globular; (b) the Nissl granules break up and lose their staining reactions; (c) the nucleus swells, stains badly, and is displaced to one edge of the cell, or it may be extruded altogether. The changes in the part of the axis cylinder still connected with the nerve cell are slight, while those in the part separated from the cell are very profound and degenerative: (a) The axis cylinder loses its fibrillation, and soon ceases to conduct impulses. It becomes

irregular through the disappearance of pieces of its substance, and then breaks up into short lengths. (b) The neurilemma thickens, its cells multiply, and the surrounding capillaries dilate. (c) The medullary sheath breaks up, and its myelin becomes collected into drops. The lecithin in these drops breaks down into its component unsaturated fatty acids, phosphoric acid, and choline. (d) Neurilemma cells, macrophages and phagocytes (from the capillaries) invade the degenerating tissues and remove the *débris* piecemeal. When this work is completed, the neurilemma cells remain and form a chain of cells which marks the path formerly taken by the degenerated axon.

REGENERATION OF NERVES. Repair first begins in the cells: (a) swelling of the cells disappears and they return to the normal shape; (b) the Nissl granules re-form; (c) the nucleus takes up its old position in the centre of the cell and its staining reactions become normal. Repair of the axon takes place as follows: From the part of the axon connected to the nerve cell neurofibrils sprout in all directions. By chemiotaxis they are attracted to the neurilemma cells of the old degenerated sheath and grow down between these cells to form a new axis cylinder. A new medullary sheath is produced, thus completing the repair. Regeneration as a rule only occurs in nerves outside the central nervous system, *i.e.* in those which have a neurilemma.

THE MAMMALIAN NERVOUS SYSTEM

Anatomically, the mammalian nervous system consists of the large mass of nerve tissue, the brain, contained in the cranial cavity, and the long narrow spinal cord from which emerge the spinal nerves. The brain may be subdivided into: (1) the pallium or cerebrum, and (2) the brain stem, which from above downwards includes (a) the ganglia at the base of the cerebrum, which are entirely hidden by it; (b) the mid-brain; (c) the cerebellum with its three peduncles; and (d) the medulla, the lower end of which connects with the spinal cord. The functions performed by each of these parts of the central nervous system will be considered in detail in the chapters which follow. Briefly, we may say that the function of the cord is principally to act as a conductor. Histologically, it consists of an H-shaped column of cells (the grey matter) surrounded by bundles of medullated axons (the white matter). Of the nerve cells, some give rise to motor axons which leave the cord and go to muscles, some to long sensory axons which convey impulses up the cord towards the cerebrum, or structures below the cerebrum, *e.g.* to the cerebellum, while some belong to short distance axons for correlating the action of neighbouring groups of muscles or for reflex acts. The medulla contains the long path axons and their accessory structures which are passing through it on their way to and from the cord. In addition it contains important 'centres' (control stations) for the heart, blood vessels, and for respiratory movements, as well as the nuclei (relay stations) of many of the cranial nerves. The cerebellum lies off the main track, and receives impulses both from the cord and medulla below and from the cerebrum above. It presides over the co-operation of muscles for the performance of skilled acts. The mid-brain lies on the main track; it also contains the relay stations of several cranial nerves. The ganglia at the base of the cerebrum act as sorting and relaying stations for impulses which are on their way to the cerebrum. They also have certain specific functions assigned to them which will be described later.

THE BRAIN STEM. It is usual in treating of the structure of the brain stem to consider it as a prolongation forwards of the spinal cord and as consisting, like this, of a central tube of grey matter surrounded by a tube of

white matter. But at the fore end of the body have been developed the organs of special sense, which are the most important in determining the reactions of the animal in response to present or approaching changes in its environment. Hence we cannot expect to find in the brain stem the regularity of arrangement of grey and white matter which is met with in the cord, and the typical division of the grey matter into cornua becomes altogether lost. While some nerves take their origin from or terminate in the central tube of grey matter, in other cases the collections of nerve cells and fibres forming the

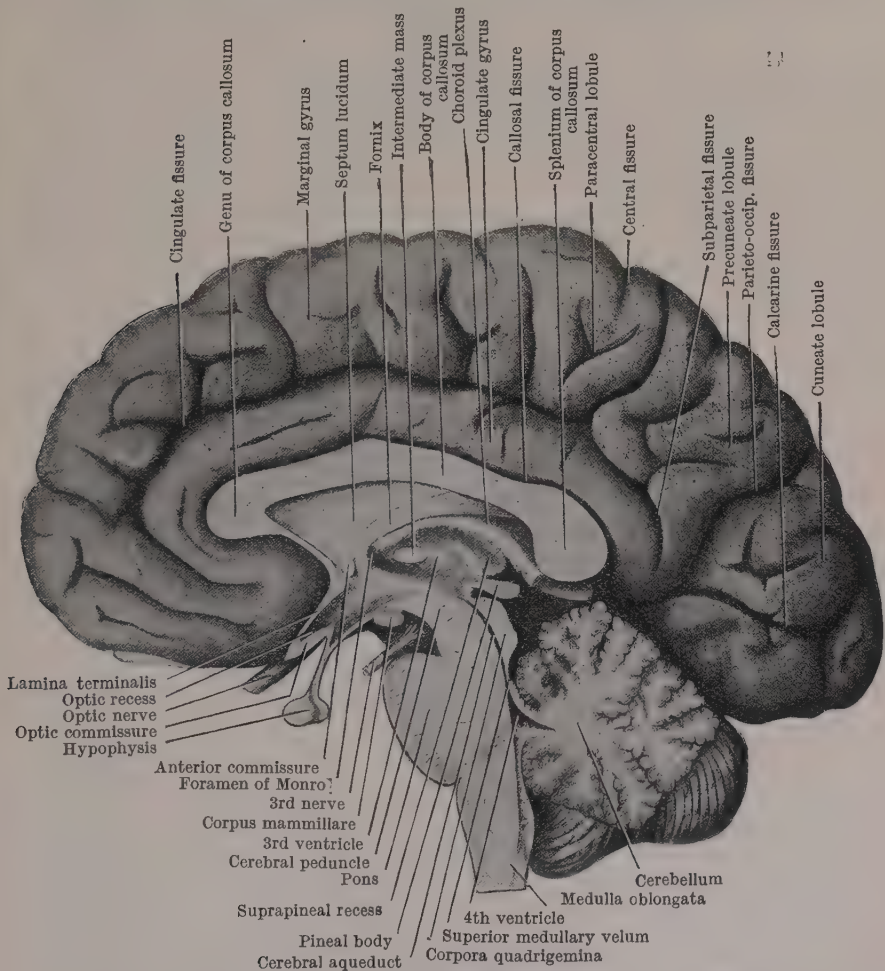


FIG. 144. Medial Section of an Adult Human Brain. (J. SYMINGTON.)

nuclei of the cranial nerves have become more or less separated from it. Moreover, the central grey matter is by itself quite inadequate to deal with the flood of ingoing impressions entering the central nervous system through the organs of special sense, or to co-ordinate these with one another, or with those arriving from the skin and lower part of the body. In consequence, masses of grey matter, which have no representatives in the cord, make their appearance, and may be regarded as additional sorting or relay stations for the various kinds of impulses which determine the nervous activities of the animal.

The anatomical relationship between the parts of the central nervous system just mentioned may be gathered from a careful study of Fig. 144. The whole of the front, the top and most of the base of the diagram are occupied by the thick, much-convoluted cerebrum, the right and left halves of which are associated by the large mass of axons forming the corpus callosum. Below this will be seen a hollow funnel-shaped mass of tissue which is narrowing as it passes downwards from cerebrum to mid-brain. In this mass the ganglia at the base of the cerebrum are situated. Past them the long path axons travel through the internal capsule, connecting cerebrum with mid-brain. The narrow neck of the mid-brain is well shown. Surrounding it like a collar is the pons which associates the two halves of the cerebellum. Below the laminated cerebellum is the medulla.

CHAPTER XV

THE CEREBRAL HEMISPHERES

THE cerebral hemispheres form the largest and most important part of the human brain. It is to the progressive evolution of this part that is due the rise in type in vertebrates. In development they are formed as two diverticula from the front part of an outgrowth of the first cerebral vesicle. In the lowest vertebrates these outgrowths are connected entirely with the olfactory sense organs, and we may regard the olfactory part of the brain as a fundamental structure on which has been built up all the rest of the cerebral hemispheres. With the increasing importance of the visual sensations in the bony fishes there is still very little corresponding growth of the fore-brain, most of the fibres from the optic nerves going to the roof of the mid-brain (the optic lobes). The beginning of the cerebral hemispheres is associated with the development of nervous tissue in the roof of the fore-brain. At its first appearance this higher brain material still receives chiefly olfactory impres-

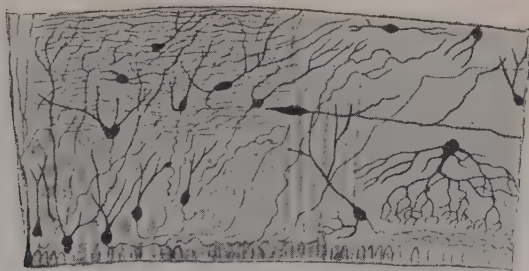


FIG. 145. Section through Cerebral Cortex of Frog. (After EDINGER.)

sions. But the structure of the cerebral cortex thus laid down differs from that of the centres forming the brain stem or the olfactory lobe itself in that it provides for a very rich association of impulses between all its parts. The fibres entering the cortex break up into a fine meshwork of fibres which run tangentially to the surface and come in relation with innumerable dendrites of nerve cells situated at some little distance below the surface (Fig. 145). We have here the first germ of an apparatus in which the nerve paths can be determined by education rather than by the limits set by heredity. In the amphibian and reptile, the cerebral cortex extends over the whole roof of the cerebral hemispheres, though even here a very large proportion of it is devoted to the association of olfactory impulses. The wider reactive powers of birds are based chiefly on an enormous development of the corpus striatum, whereas in mammals the corpus striatum remains relatively small, and the chief development occurs in the roof of the cerebral hemispheres. With the increased entry of fibres from the optic thalamus into the cerebral hemispheres, carrying impulses from the eyes, ears, and all the other sense organs of the body, the olfactory part of the brain diminishes in importance, and in

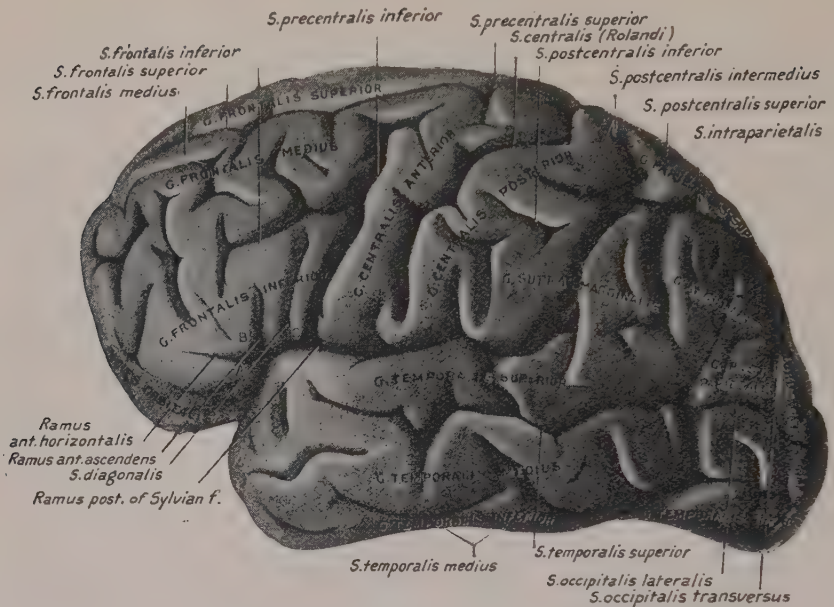


FIG. 146. Left Cerebral Hemisphere of Man. Lateral aspect. (SYMINGTON.)

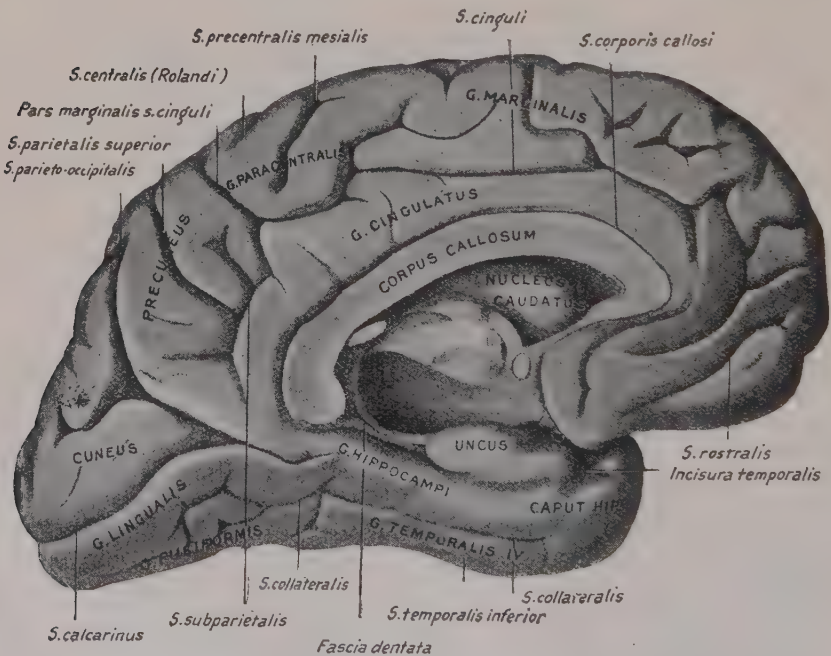


FIG. 147. Left Cerebral Hemisphere of Man. Mesial aspect. (SYMINGTON.)

the higher mammals and man is altogether overshadowed by the newly-formed structures of the cerebrum.

In man, the cerebral hemispheres form a great ovoid mass, exceeding in size all the rest of the brain put together. The two hemispheres are

separated by a deep fissure, the great longitudinal fissure. Before and behind, this fissure extends to the base of the cerebrum, but in the middle the two hemispheres are connected by a mass of transverse fibres known as the *corpus callosum*. On the outer side each cerebral hemisphere presents a deep cleft, the *Sylvian fissure*. The whole surface of the brain is thrown by fissures (or sulci) into convolutions, by which means a very large increase of the surface grey matter is obtained. By these fissures the brain surface is divided into lobes. The general arrangement is shown in Figs. 146, 147.

The chief lobes are (a) the frontal, to which are ascribed voluntary movements; (b) the parietal, to which are ascribed skin sensations of various kinds; (c) the calcarine, for vision; (d) the temporal, for hearing; (e) the limbic area for taste and smell. The chief fissures separating these are (a) the central or fissure of Rolando, between frontal and parietal lobes. Motor fibres to the body start just in front of, and sensory fibres from the limbs end just behind this fissure, which may be said to be the most important on the cerebrum; (b) the Sylvian fissure between the parietal and temporal; (c) the parieto-occipital; (d) the calloso-marginal, forming the outer boundary of the limbic area.

Each of the main lobes or areas mentioned above is further subdivided by numerous fissures less important than those just mentioned. Not only does their number differ between monkeys and man, but even between different races of men, the higher types of brain being richer in convolutions. In any one brain the two halves are very nearly but not quite alike, either in weight or in the position of the convolutions. On the average, a man's brain is, in conformity with his greater body weight, heavier and more convoluted than a woman's.

MINUTE STRUCTURE OF THE CEREBRAL CORTEX. The cortex of the cerebral hemispheres consists of a layer of grey matter covering a central mass of white fibres. With the growth in size of the brain which accompanies the development of increased intelligence and powers of adaptation, the necessary increase in cortex is rendered possible by the folding of the surface into convolutions and fissures.

On section the fresh cerebral cortex is seen by the naked eye to consist of two main parts, a thin superficial grey part, and a thick white part placed beneath it. Examination in different regions will show that the naked eye appearances differ from place to place.

On section the grey matter is seen to consist of many layers of nerve cells embedded in neuroglia and nerve fibres, both medullated and non-medullated. The nerve cells vary in size and shape; one kind of cell typical of the cerebral cortex is the *pyramidal cell*, a cone-shaped cell with one large apical dendrite which runs towards the surface and breaks up in the most superficial layer into a number of branches. Dendrites are also given off from the sides and lower angles of the cell. The axon, which arises from the axon hillock in the middle of the base of the cell, passes downwards into the white matter, giving off small collaterals in its course. Some of these axons, including those which form the pyramidal tracts, pass by the corona radiata through the internal capsule and into the crura cerebri. Others, or their collaterals, may pass into the adjacent regions of the cortex, or may pass by the corpus callosum into the opposite cerebral hemisphere. Although varying in structure in different parts, it is generally possible to distinguish eight layers in the grey matter of the cortex (Fig. 148).

(1) The superficial plexiform layer. It contains few cells, and is composed principally of the dendritic endings of cells belonging to deeper layers. It contains a few horizontal cells of Cajal. These have several processes which

run approximately parallel to the surface. It is probable that afferent fibres entering the cortex pass up towards the surface and end for a large part in this molecular layer.

(2) The layer of small pyramidal cells. In addition to these are found small granule cells and double brush cells.

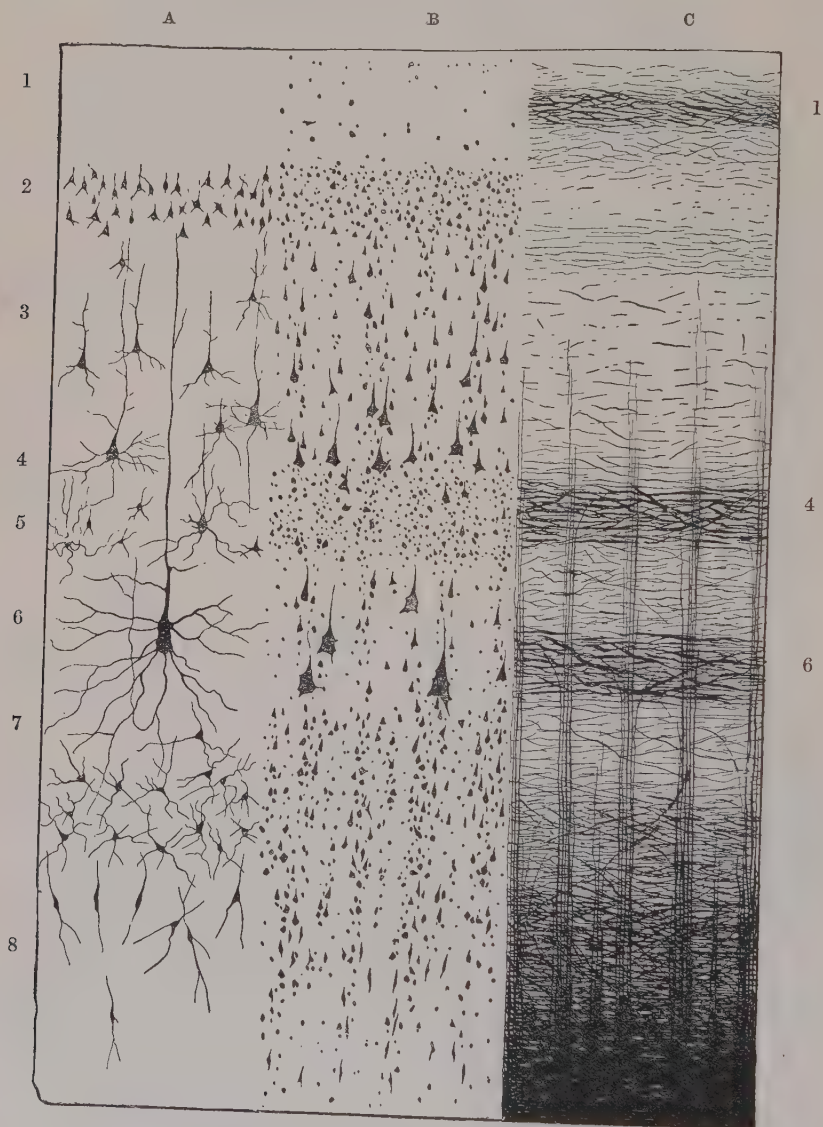


FIG. 148. Diagram of the Layers of Cells and Fibres in the Grey Matter of the Human Cerebral Cortex, stained by three different methods: A. Golgi; B. Nissl; C. Weigert. (After LUCIANI'S "Physiology," MACMILLAN.)

(3) The outer layer of medium pyramidal cells. Here also granule cells and double brush cells are found.

(4) The outer layer of large pyramidal cells.

(5) The layer of stellate cells. Sometimes this layer is called the middle stellate or granule layer.

(6) The inner layer of large pyramidal cells. It is in this layer of the motor area that the giant Betz cells are found.

(7) The inner layer of medium pyramidal cells.

(8) The fusiform cell layer which is particularly marked in the claustrum.

Internal to this eighth layer is found the white matter of the cerebral hemisphere.

The pyramidal cells of all sizes possess, in general, three different kinds of fibre: an apical one, which runs towards the external surface, and then branches tangentially to the surface; a basal one running towards the white matter, where it becomes medullated and runs a variable distance according to its function; and a series of transverse ones which run tangentially. In consequence, these tangential fibres form well-marked lines, particularly where the two large pyramidal cell layers occur (Layers Nos. 4 and 6 above). In consequence, if sections of the cortex are stained by a method like Weigert's, which displays the nerve fibres, sheaves of radial fibres will be seen running from the white matter towards the surface, giving off a rich meshwork of fibres to the intervening portions of the grey matter, while the bands of tangential fibres are seen running parallel to the surface. Thus we find:

(1) the tangential fibre layer which corresponds to the plexiform layer; (2) the outer radial fibre layer, sometimes called the band of Bechterew; (3) the outer radial fibre layer, corresponding to the outer layer of medium pyramidal cells; (4) the outer layer of tangential fibres corresponding to the large pyramidal cell layer. This is sometimes called the outer line of Baillarger; (5) the middle radial fibre layer, corresponding to the stellate cell layer; (6) the inner line of tangential fibres, corresponding to the inner layer of large pyramidal cells, sometimes called the inner line of Baillarger; (7) the inner radial fibre layer, which corresponds to layers (7) and (8), namely, the medium pyramidal cell layer and the fusiform cell layer. The radial layers are formed partly of apical and basal fibres of the various cells seen in the section, and partly of fibres which have travelled to the cerebral cortex in order to ramify there.

About 90 per cent. of the area of the cortex in man shows all the above layers at some stage in its embryonic development; about 60 per cent. of the cortex retains this structure when fully developed; about 10 per cent., *e.g.* the calcarine cortex, becomes still more elaborate; while about 20 per cent., the voluntary motor area, becomes simplified. Only about 10 per cent., namely, the hippocampus (for smell), does not show at any stage all the above layers.

A careful study of the histology of the different parts of the cortex in man enables us to recognise many different areas, which differ from one another in the following respects: (a) The relative thickness of the different layers of the cortex; (b) its total thickness; (c) the character of the cells found in the different layers; (d) the arrangement and degree of development of the systems of medullated fibres, both radial and transverse. According to the plan of classification used, some ten to fifty different cortical areas may be distinguished, each with specified arrangements of cells and fibres assigned to them. Some of the more important differences are these: (1) In the motor area, layers (4), (5), and (6) have lost their demarcation and are occupied by giant Betz cells, the axons of which form the pyramidal tract. (2) In the visual area the pyramidal cell layers are thin, the large pyramidal cells being very few. The lines of Baillarger are very distinct, particularly the outer, which is sometimes called the line of Gennari, a characteristic of this region. (3) In the olfactory area (hippocampus) the cells are arranged in three groups, an outer polymorphic layer, a middle fusiform cell layer, and

an inner polymorphic layer. By a similar method a comparison of the probable cerebral functions of different types of animal may be made. While in dog, ape, and man the absolute amount of brain substance devoted to the elementary functions of movement and sensation remains practically the same, in man these areas are relatively very much diminished in size, and the greater part of the brain surface is taken up by nervous material of the type which is connected with the functions of association involved in the higher processes of reflection and intelligence.

THE CHIEF TRACTS OF THE CEREBRAL HEMISPHERES

We may divide the tracts of the cerebral hemispheres into three classes:

I. Tracts connecting the brain with lower levels of the central nervous system: the projection fibres.

II. Tracts connecting the different parts of the cortex of the same hemisphere and serving as a means of association between these different parts.

III. Commissural tracts, connecting the two cerebral hemispheres.

I. THE PROJECTION FIBRES. These are the fibres which connect the cerebral cortex with the lower levels of the central nervous system. They form a great part of the fibres composing the corona radiata, and at the base of the brain are condensed into the broad band of fibres known as the *internal capsule*. A few of the fibres of the projection system may reach the cortex through the lenticular nucleus and by the external capsule.

The projection fibres may be divided into two great groups according as they conduct impulses to or from the cerebral cortex. Thus, the anterior parts of the corona radiata and internal capsule are formed (a) of fibres running from the frontal lobe to the cerebellum *via* the pons, and (b) of fibres which, ascending from lower parts of the central nervous system, have relayed at the optic thalamus. These parts of the corona radiata and internal capsule thus contain both fibres from and fibres to the cortex.

The superior parts of the corona radiata and middle part of the internal capsule are formed (a) of fibres which, ascending from lower parts of the central nervous system, have relayed at the optic thalamus, and are going to the post-central sensory area; (b) of fibres which, starting from the Betz cells in the præcentral motor area, are passing down as the pyramidal tract which is used for voluntary movement.

The posterior parts of the corona radiata and internal capsule are formed (a) of fibres which comprised the optic tracts and have relayed in the external geniculate body of the optic thalamus. They convey visual sensations to the calcarine cortex; (b) of fibres which travel to the retinae of the eyes from the calcarine region.

The inferior parts of the corona radiata and postero-external parts of the internal capsule are formed (a) of fibres which have relayed in the internal geniculate body, and are conveying auditory sensations to the cortex of the temporal lobes; (b) of fibres which, leaving the temporal lobes, pass down to the cerebellum *via* the pons.

Anatomically, there is no demarcation between these sets of fibres. They form, rather, a continuous sheet of medullated axons which, sweeping downwards and inwards from all parts of the cerebral cortex, converge on their passage through the internal capsule, and thus pass downwards to the lower parts of the central nervous system.

The relative position of these various fibres in the internal capsule and in the crusta, is shown in Fig. 149.

The fronto-pontine and temporo-pontine fibres end by anastomosing round cells which form the nuclei pontis; the axons of these cells form part of the pons, the middle peduncle of the cerebellum. The axons end chiefly in the lateral lobes of the cerebellum. These fibres may therefore be regarded as the descending part of the great cerebro-cerebellar pathway of which the ascending part is represented by the fibres which pass from the cerebellar cortex to the dentate nucleus, and thence by fresh relays up the superior cerebellar peduncles, crossing to the optic thalamus of the other side. The cells there give off axons which convey the impulses to the

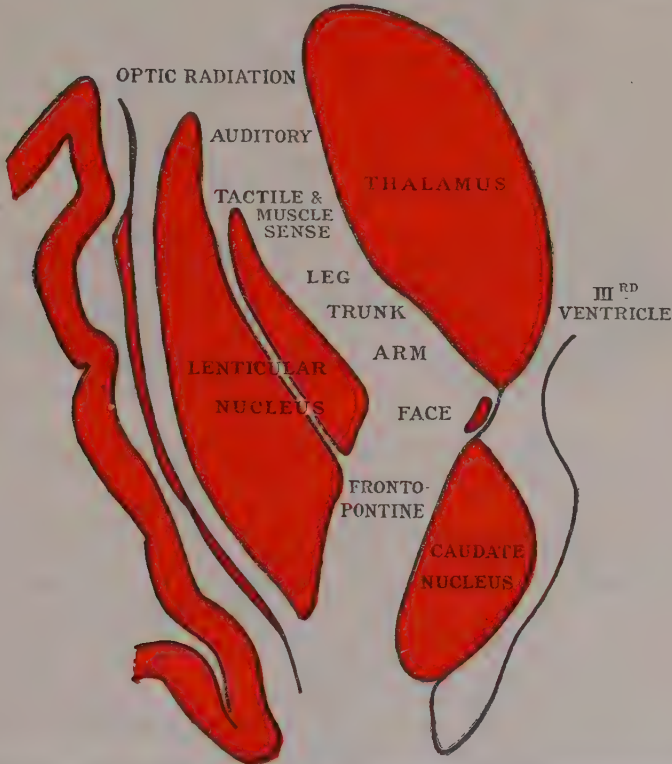


FIG. 149. Diagram of the Right Internal Capsule, as seen in horizontal section.
(BAINBRIDGE AND MENZIES' "Physiology.")

cortex. The development of these fibres, as of the lateral lobes of the cerebellum, is largely proportional to the growth of the cerebral hemispheres. In cases where there has been congenital atrophy of one cerebral hemisphere, the crusta of the same side and the lateral lobe of the cerebellum of the opposite side also fail to develop.

II. THE COMMISSURAL FIBRES. These are arranged in three groups :—

(1) *The Corpus Callosum* forms the great mass of white fibres passing transversely in both directions between the two hemispheres. Its fibres are derived from every part of the cerebral cortex with the exception of the olfactory bulb and the hind and fore parts of the temporal lobe. As the fibres cross the middle line they become gradually scattered, so that they tend to connect wholly dissimilar parts of the cortex of opposite hemispheres. Each callosal fibre may represent either the axon of one of the cortical cells or a

collateral from a fibre of association or from a projection fibre. It arises in one hemisphere and ends by fine arborisations in the opposite hemisphere.

(2) *The anterior commissure* is situated in the anterior wall of the third ventricle in front of the two pillars of the fornix. It connects the two olfactory lobes and portions of the opposite temporal lobes. In lower vertebrates it is almost entirely olfactory in function, but in man the olfactory fibres form only a small proportion of the total number making up the bundle.

(3) *The hippocampal commissure*, joining the two hippocampal areas (for sense of smell).

III. ASSOCIATION FIBRES. These fibres serve to unite different portions of the cortex of the same hemisphere and may be classified into short and long association fibres (Fig. 150). The short association fibres pass round the bottom of the sulci in U-shaped loops connecting adjacent convolutions. These fibres are some of the latest to acquire a medullary sheath and probably

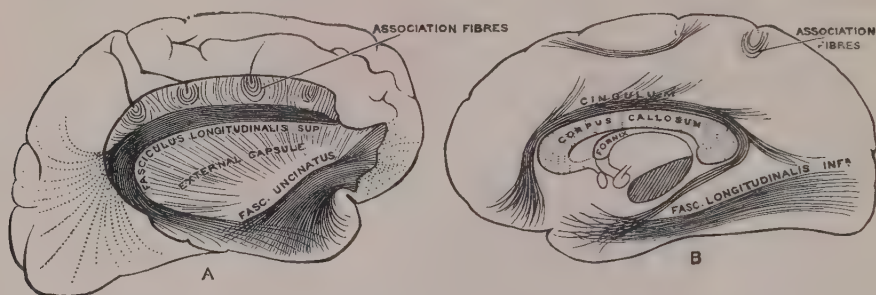


FIG. 150. Chief Association Bundles of the Cerebral Hemispheres. (CUNNINGHAM.)
A. Outer aspect of hemisphere. B. Inner aspect of hemisphere.

first become functional as associated activity between the various portions of the cortex is gradually acquired by education.

The long association fibres may be divided into five groups as follows :—

(1) *The uncinate fasciculus*, from the frontal lobe to the temporal lobe round the stem of the Sylvian fissure.

(2) *The cingulum*, passing from front to back, runs over the top of the corpus callosum, branching all the way.

(3) *The longitudinal superior fasciculus* connects the temporal with the frontal and occipital parts of the cerebral cortex.

(4) *The longitudinal inferior fasciculus* runs along the whole length of the occipital and temporal lobes, being situated behind on the outer aspect of the optic radiation.

(5) *The occipito-frontal fasciculus* lies on the inner aspect of the corona radiata in intimate relation to the caudate nucleus, and connects frontal and occipital lobes.

THE FUNCTIONS OF THE CEREBRAL HEMISPHERES. The old views of the phrenologists were that the mind consisted of faculties, each of which inhabited a fixed place in the cerebral cortex and, if markedly present, caused a bump which could be felt under the skin. These views had to be abandoned as the result of experience and experiment. Instead, we assign the various cortical areas to motion, sensation, hearing, vision, etc. May we then say that love, hatred, impetuosity, or greed find no place in the cortex ? The answer is, only as associated ideas. With this subject we shall deal later.

An animal, such as the dog or rabbit, which has been deprived of its cerebral hemispheres, still shows motor and other reflexes. It still preserves the whole mechanism for the maintenance of posture, for the carrying out of co-ordinated movements, for emotional expression, as well as for the various visceral functions. Yet such an animal can in no sense be regarded as normal. The decerebrate dog is lacking in all those reactions (conditioned reflexes) which have arisen as the result of individual experience. There is no recognition or seeking out of food, though the animal eats what is given him with avidity. There is no reaction to the sight of the attendant who feeds him, nor to threatening with a whip, though an actual blow evokes the emotional reflex of snarling. Such a comparison of a normal with a decerebrate animal points at once to the cerebral hemispheres as the organs of learnt reactions, *i.e.* reactions which are determined, not by a congenital and immutable disposition of nerve tracts, but by the previous history of the animal. From the time of the birth of an animal with cerebral hemispheres, every change in the external world which impinges on the animal's surface can be regarded as an act of education, in that it is instituting new modes of reaction or altering those which have been previously attained. In consequence of this the study of the function of the cortex is by no means simple. The following methods have been employed:—

- (a) Pavlov's method of conditioned reflexes (Chapter XX.).
- (b) Removal of part of the cortex of an animal and noting the change in behaviour after recovery from the immediate results of the operation.
- (c) Correlating the behaviour of a man who has disease of the "brain" with the pathological changes found post-mortem.
- (d) Stimulation by electric currents of the cortex of an animal under an anaesthetic.
- (e) Similar observations on man following, *e.g.* accidental fracture of the skull.
- (f) By the histological method (1) on adult uninjured tissue, or (2) by the previous cutting of tracts and the following of the degenerated fibres, or (3) by following the order in which the fibres obtain myelin sheaths during the development of the embryo. Further reference will be made to these methods and the results obtained by them when dealing with the different areas of the cerebral cortex in the chapters which follow.

RELATION OF THE CEREBRUM TO OTHER PARTS OF THE CENTRAL NERVOUS SYSTEM

THE BASAL GANGLIA. It is intended in the chapters which follow to describe the central nervous system from its physiological aspect. But it is necessary for there to be a precise knowledge of the anatomical positions of the principal constituent nuclei and the course taken by the fibres which connect them.

The internal capsule is composed of medullated axons which pass downwards and inwards through the corona radiata from all parts of the cerebral cortex, the right-hand and left-hand capsules making an angle with one another. That this is approximately a right angle will be seen from Fig. 151. Again, the corpus callosum runs horizontally, joining right and left hemispheres, and there are thus two conical areas lying between it and the two capsules. These areas are occupied partly by the "T"-shaped space, called the lateral and third ventricles, which contains cerebrospinal fluid, and partly by the optic thalamus and the caudate nucleus. Below the capsules are two other conical areas. These are occupied by the putamen and globus pallidus,

which together constitute the lenticular nucleus. The caudate and lenticular nuclei are collectively called the corpus striatum.

A horizontal section through the cerebrum shows the relative positions of these nuclei well (see Fig. 149).

THE MID-BRAIN. During their passage through the corona radiata, ascending and descending fibres have been running side by side. As they approach the internal capsule a separation takes place. Since the ascending ones have all relayed in different parts of the optic thalamus, and this lies internal to and above the internal capsule, it follows that the fibres emerging from the optic thalamus (that is, the ascending fibres) lie above those (the descending) which are passing down into the internal capsule. This separation is retained in the mid-brain, and with local modifications can be seen retained throughout the whole length of the central nervous system. Posteriorly lie the ascending and anteriorly lie the descending fibres. Since

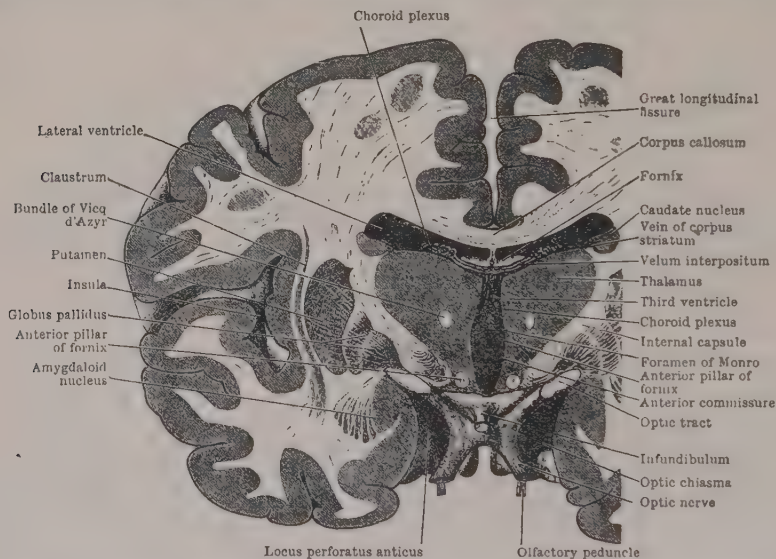


FIG. 151. Coronal Section through the Cerebrum so as to cut through the three divisions of the Lenticular Nucleus; Posterior surface of the section depicted. (CUNNINGHAM.)

the ascending are usually coming from sense organs of one kind or another, and since the descending go usually to spinal centres for the muscles, the 'sensory' fibres are sometimes referred to as lying posterior to the 'motor' ones. We find, then, the greater part of the mid-brain occupied by these ascending and descending bundles, and, as we should expect from what has been just written, the descending lie anteriorly.

In addition, we find two pairs of elevations on the posterior aspect: (a) The superior corpora quadrigemina (colliculi), which are part of the motor path to the eye muscles; (b) the inferior corpora quadrigemina (colliculi), which are part of the path for hearing.

Lastly, there are two important postero-internal landmarks, the red nuclei and the superior cerebellar peduncles. Both these form part of the main path connecting the cerebellum with the muscles of the limbs, &c., for synergic (co-operative) control. *Via* the superior cerebellar peduncles highly important fibres also pass between the cerebellum and the cerebrum, effecting mutual co-operation.

THE CEREBELLUM. On the anterior aspect in this region we find, as we should expect, the fibres which descend in the mid-brain, and posterior to them the ascending ones. But encircling them on all sides we find structures which belong to the cerebellum. Behind are parts of the cerebellum itself, while to the sides and in front are the fibres of the pons, which acts to the cerebellum as the corpus callosum to the cerebrum, that is, its fibres connect

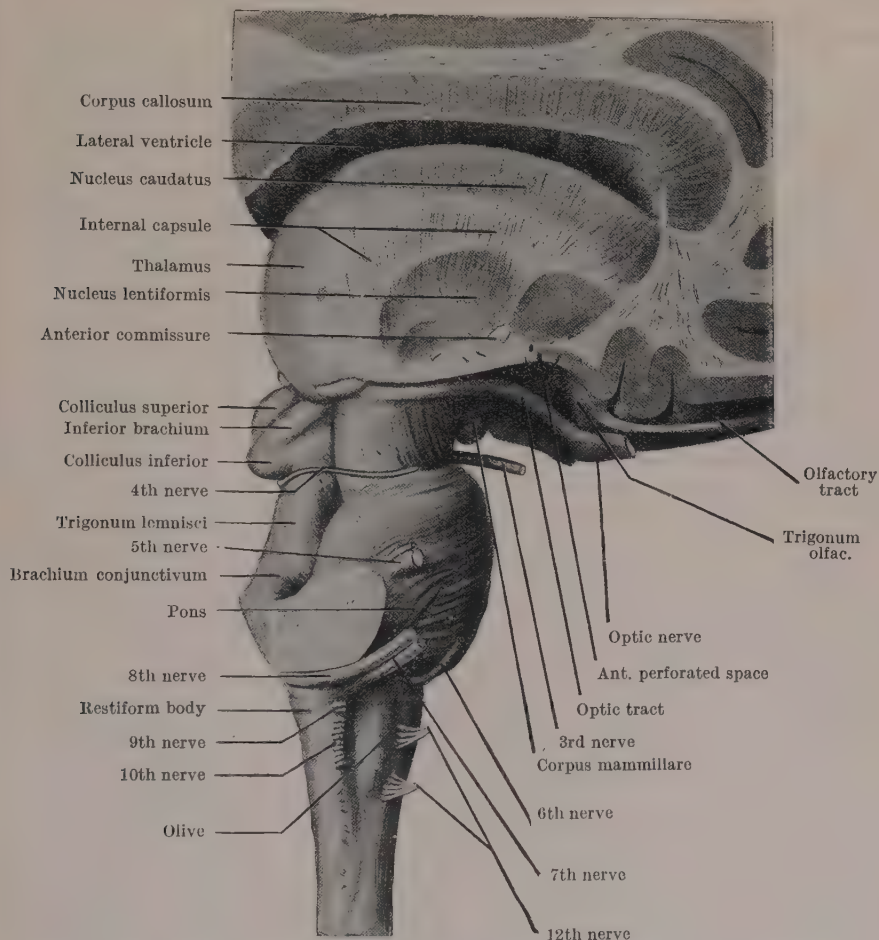


FIG. 152. Right Lateral Aspect of Brain Stem, with front of the Cerebrum.
(J. SYMINGTON.)

the right and left halves of this organ. As we shall see later, many cranial nerves leave at or near this level (see Fig. 152).

THE MEDULLA. In this region two important changes occur, one in the ascending and one in the descending fibres. At the top of the medulla, as we have seen, the ascending fibres are behind and the descending ones in front. At the bottom of the medulla this is still their approximate position, but with the important difference that the greater part of both sets of fibres have crossed over to the other side. Those connected with the right-hand side of the cerebrum are on the right at the top of the medulla, but most of them have crossed to the left before the lower end of the medulla is reached. These crossings affect ascending and descending fibres separately, the sensory

decussation occurring at a higher level in the medulla than the motor. These decussations form, therefore, highly important landmarks. Very important also are the cranial nerves which originate in this region and the centres to which they connect, centres which control the heart, the circulatory system, and respiration. Each of these functions will be dealt with in the sections which follow.

CHAPTER XVI

THE SPINAL CORD

IN man the spinal cord is an elongated cylindrical structure, slightly flattened from before backwards, and about half a metre long. It gives off a series of nerve roots, which are arranged in thirty-one pairs, and are placed symmetrically on either side. Each nerve has two roots, an anterior or ventral motor root and a posterior or dorsal sensory root. The ventral roots are efferent in function, and the dorsal ones afferent. A mixed nerve consists of fibres which are connected to both these roots. The anterior fibres spring from the cord in a series of rootlets; the posterior fibres pass first to the posterior root ganglion and then enter the cord as a compact bundle. On section the cord is seen to consist of an H-shaped core of grey matter surrounded on all sides by white matter. The former is composed of nerve cells, the latter is made up of medullated nerve fibres which are devoid of neurilemma and are connected into bundles held together by neuroglia. On the anterior aspect of the cord is a furrow, the anterior fissure, and on its posterior aspect is another fissure, which is deeper and narrower than the anterior one. In the centre of the band of grey matter which connects the two masses of grey matter on either side of the cord is the central canal, which is the remains of the primitive neural canal of the embryo. Since nerves enter and leave the cord in greatly increased numbers at those segments which correspond to the arm and leg, the grey matter is greatly increased at these two situations, forming the cervical and lumbar enlargements. On the other hand, since the white matter consists of conductors which are conveying impulses from the brain down the cord and *vice versa*, the white matter is found to diminish progressively in amount as one proceeds downwards, since the neck region will contain fibres which are connected with many segments, while the lower part contains the fibres which are destined for a fewer number of segments.

Bearing these facts in mind, we can distinguish sections which have been taken from different parts of the cord. In the cervical region there will be large bundles of white matter, and grey matter will also be much in evidence. Fig. 153 shows that the cervical region is oval in section. In the dorsal region white matter is also much in evidence, but the amount of grey matter is small and the cord is nearly circular in section. In the lumbar region, where the nerves to the lower limbs are being produced, the grey matter is much in evidence, but the amount of white matter is relatively smaller.

THE NERVE CELLS OF THE CORD.

Nerve cells are arranged in the grey matter of the cord in several distinct groups. Near the posterior horn are found masses of small richly-branched nerve cells, which are spoken of as the *substantia gelatinosa Rolandi*. Near the anterior horn three groups of cells may be distinguished, a median group which send their processes across to the other side in the anterior white commissure; an external group, consisting of multipolar cells which send fibres out at the anterior horn; a third group, most marked in the cervical and lumbar enlargements, consisting of very large multipolar cells with

system. In the dorsal region of the cord on the inner aspect of the posterior horn is found the column of cells known as Clarke's column. In addition to the motor anterior horn cells, the commissural cells, the cells of Clarke's column, and those of the substantia gelatinosa Rolandi, there are cells of Golgi, which are found chiefly in the posterior horn. They are multipolar cells and are distinguished by the fact that their axons travel but a short distance and then break up into branches. They probably associate the functions of neighbouring segments.

THE NERVE FIBRES OF THE SPINAL CORD.

These may be divided into three groups : (i) Long path axons, such as those forming the tracts of the posterior columns, *i.e.* the tracts of Goll and Burdach (fasciculus gracilis and fasciculus cuneatus), or those forming the pyramidal tracts; (ii) association fibres which connect neighbouring segments; and (iii) commissural fibres, which enable opposite halves of similar segments of the spinal cord to co-operate.

A further classification is into ascending and descending tracts. These, chiefly long path tracts, will now be briefly described.

I. ASCENDING TRACTS. (a) The sensory fibres for pain, temperature and touch, pass through the posterior root ganglion and enter the posterior root. They ascend a short distance in Lissauer's tract (4, Fig. 154), and relay in the cells of the substantia gelatinosa Rolandi. Second order fibres originating in these cells cross near the central canal to form part of the spino-thalamic tract. In this they ascend to the optic thalamus, where they relay round third order cells which convey the impulses to the cortex. (11 and 13, Fig. 154.)

(b) Kinæsthetic sensations enter at the posterior root, ascend in the columns of Goll and Burdach until they reach the nucleus gracilis and nucleus cuneatus in the medulla. The cells in these nuclei give off second order relay fibres which, crossing in the sensory decussation, ascend in the lemniscus (fillet) to the optic thalamus. Third order fibres originating in this convey the impulses to the cortex. (6 and 7, Fig. 154.)

(c) Kinæsthetic skin sensations destined for the cerebellum enter the posterior root, and ascend in Goll and Burdach to the nucleus gracilis and nucleus cuneatus; second order fibres originate from the cells in these nuclei to travel as superficial or deep arcuate fibres to the inferior cerebellar peduncle by which they reach the vermis. Third order fibres then convey the impulses to the cerebellar cortex.

(d) Kinæsthetic impulses from muscles, destined for the cerebellum, enter the posterior root and go to Clarke's column; from the cells in this column second order fibres either ascend in the direct cerebellar tract and, entering by the inferior cerebellar peduncle, go to the vermis, from which third order fibres convey the impulses to the cerebellar cortex; or they may cross to the opposite side, and ascend in the indirect (crossed) cerebellar tract to the level of the red nucleus. They then descend abruptly to enter the superior cerebellar peduncle, in which they cross once more to reach the vermis on the same side as that on which they started. From this, third order fibres travel to the cerebellar cortex. (8 and 12, Fig. 154.)

II. DESCENDING TRACTS.—(a) Those for voluntary movement start in the precentral motor cortex; second order fibres commencing from the Betz cells pass down through internal capsule and pons to reach the medulla. Here part of the fibres cross, forming the motor decussation; part descend uncrossed. The crossed fibres form the cerebro-spinalis lateralis or crossed pyramidal tract; they end at anterior horn cells, from

which third order fibres convey the impulses to the muscles. Those which do not cross travel in the direct pyramidal or cerebro-spinalis anterior tract, cross near their terminations to anterior horn cells of the opposite side, from which third order fibres convey the impulses to the muscles. Thus, all fibres from the right motor cortex are distributed to the left side of the cord. (9 and 17, Fig. 154.)

(b) Impulses for group movements probably travel in the rubro-spinal

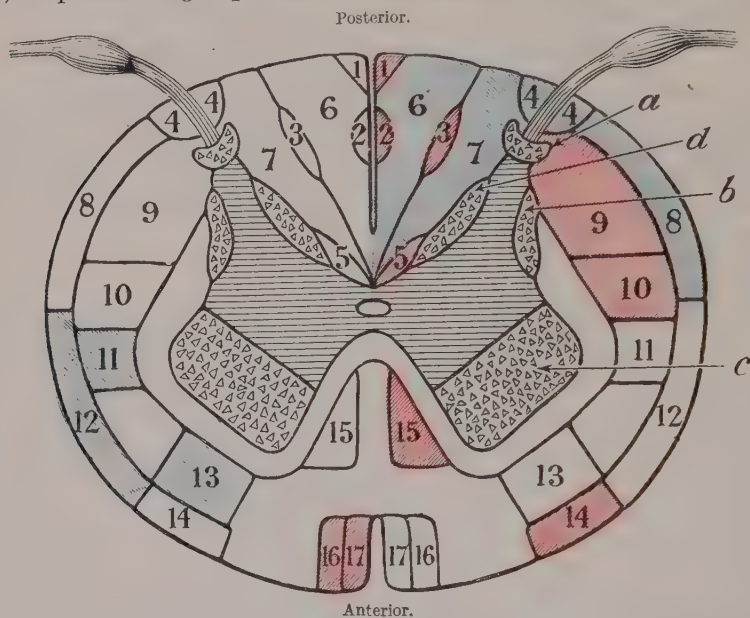


FIG. 154. Diagrams showing Position of Tracts of the Cord. All coloured tracts convey impulses to or from the right-hand spinal nerves. Ascending tracts are blue. Descending tracts are red.

(1) Triangular bundle. Short descending tract. (2) Oval bundle of Flechsig. Short descending tract for spinal association. (3) Comma tract. Short descending tract for spinal association. (4) Lissauer's tract. Short ascending tract for pain, temperature and touch. (5) Cornu commissural tract. Short descending tract for spinal association. (6) Posterior column of Goll. Long ascending tract for limb sensation. (7) Posterior column of Burdach. Long ascending tract for limb sensation. (8) Direct spino-cerebellar tract. Long ascending tract for group movement association. (9) Crossed (cerebro-spinal) pyramidal tract. Long descending tract for voluntary movement. (10) Rubro-spinal tract. Long descending tract for group movement. (11) Lateral spino-thalamo-cortical tract. Long ascending tract for temperature and pain sensations. (12) Crossed spino-cerebellar tract. Long ascending tract for group movement association. (13) Anterior spino-thalamo-cortical tract. Long ascending tract for touch sensations. (14) Crossed vestibulo-(Deitero-) spinal tract. Long descending tract for equilibrium. (15) Tecto-spinal tract. Long descending tract for eye protection. (16) Uncrossed vestibulo-(Deitero-) spinal tract. Long descending tract for equilibrium. (17) Uncrossed (cerebro-spinal) pyramidal tract. Long descending tract for voluntary movement. (a) Cells of substantia gelatinosa Rolandi; (b) Intermedio-lateral cell column; (c) Cells of anterior horn; (d) Cells of Clarke's column. (BAINBRIDGE AND MENZIES' "Physiology.")

tract. Leaving the red nucleus, they cross to the opposite side, and descend till they reach different levels of the cord, where they finish at anterior horn cells. These give off third order relay fibres to the muscles. (10, Fig. 154.)

(c) Equilibrium control, vestibulo-spinal tract. First order fibres travel from the hair cells of the vestibular organs to Deiters' nucleus. The cells in

this nucleus give off second order fibres which descend to the anterior horn cells in the cord. The third order fibres convey the impulses to the muscles. (14 and 16, Fig. 154.)

(d) Eye protection movements. These travel in the tecto-spinal tract. As the result of impulses reaching the calcarine cortex, fresh impulses are transmitted to the superior corpora quadrigemina (colliculus superior) by first order relay fibres. Thence, second order fibres proceed downwards and cross, forming the tecto-spinal tract by which they reach the anterior horn cells. Third order fibres now convey the impulses to the muscles. (15, Fig. 154.)

(e) The pupil dilating fibres. These fibres probably originate in the superior corpora quadrigemina (superior colliculi). They descend as far as the eighth cervical or first dorsal nerve roots. Here they probably relay at lateral horn cells, from which white rami proceed out at the anterior horn to travel to the first thoracic ganglion. They then travel up the sympathetic chain to branch off to the eyeballs, which they enter as either short or long ciliary nerves. They then travel in the perichoroidal space to the dilator muscle of the pupil.

(f) The vaso-motor fibres. These travel down the cord from the vaso-motor centre in the medulla by an unknown route. They relay in the lateral horn cells. Fibres from these cells pass out at the anterior horn, forming part of the white rami communicantes to the sympathetic. They relay in the sympathetic chain and the impulses are conveyed by unmyelinated grey rami, which join the spinal nerves and are distributed to the blood vessels.

(g) Short path ascending fibres (1, Fig. 154), a triangular bundle found in the lower lumbar region; (2, Fig. 154) the oval bundle of Flechsig, found in the lumbar region; (3, Fig. 154) the comma tract, found in the thoracic region; and (5, Fig. 154) the cornu commissural bundle of Bruce, found in the cervical region.

EFFECTS OF SECTION OF CORD AND ROOTS.

COMPLETE SECTION OF THE CORD. Complete section of the cord results in a condition known as spinal shock. While the parts of the body are apparently quite normal, there is a profound condition of paralysis of all nerves below the lesion. Thus, a monkey which has suffered a section of its lower cervical region will have profound paralysis of the lower limbs and part of the trunk, while parts above the section are apparently quite normal. The animal may contentedly direct its gaze to sights seen through the window or may amuse itself by catching flies on the pane. The condition of shock below the lesion passes off and we then find: (1) complete loss of all true sensations in parts of the body below the lesion; (2) complete paralysis of all muscles supplied by nerves below the lesion; (3) increased postural tone in all muscles supplied by nerves below the lesion; (4) reflexes such as micturition and defæcation become automatic after a period of paralysis; (5) pain referred to parts of the body below the section, if there is irritation to the cut ends of the sensory nerves which serve those parts; (6) temporary vasodilatation below the lesion; (7) a constricted pupil, owing to paralysis of the pupil-dilating fibres if the cervical region of the cord has been affected by the lesion. If the lesion is high up the cord ('spinal animal') experiment shows that a number of reflexes can be elicited. For example, the scratch reflex, a rhythmic flexion and extension of one hind leg, follows electrical stimulation of a suitable part of the flank. If the foot of one leg be pricked with a needle, there is flexion of that leg (flexor reflex), accompanied by extension of the opposite hind limb (the crossed extensor reflex). Gentle pressure

applied to one foot causes this foot to become extended and the opposite limb makes a corresponding movement of flexion.

HEMI-SECTION OF THE CORD. The symptoms that follow such a lesion were first described by Brown-Séquard, and are: (1) complete paralysis of muscles below the lesion on the same side; (2) increased postural tone and reflexes in muscles below the lesion on the same side; (3) pain, temperature, and some sensibility to touch is lost on the opposite side below the lesion; (4) kinæsthetic sensations are lost on the same side below the lesion; (5) temporary vaso-motor paralysis, and therefore a higher temperature below the lesion on the same side. In addition, there may be pain referred to parts of the body below the section as a result of irritation of the cut sensory fibres. These sensations are referred to the opposite side of the body to that on which the lesion of the cord has occurred. If the lesion has destroyed a length of the spinal cord, then in addition to the above we shall have the symptoms of damage to the anterior and posterior nerve roots which we shall now describe.

SECTION OF THE POSTERIOR ROOTS causes: (1) loss of all sensations from the limbs supplied; (2) inco-ordinated movements of the

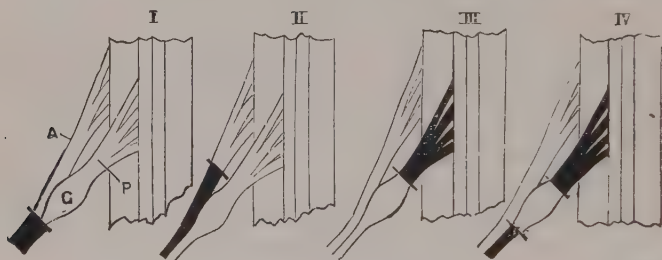


FIG. 155. To illustrate the extent and direction of degeneration as a result of Section of the Spinal Roots. (From YEO.)

Division of: I, Whole nerve trunk, below ganglion; II, anterior root; III, posterior root above ganglion; IV, posterior root above and below ganglion.

muscles owing to inability to receive kinæsthetic sensations from them; (3) injuries to the skin of the limbs supplied, owing to the absence of protective sensory impulses; (4) complete loss of tone in muscles of limbs supplied, since the kinæsthetic impulses which are responsible for them do not reach the anterior horn cells. If the section has been between the posterior root ganglion and the spinal cord, the degenerative changes affect the fibres entering the cord. If, on the other hand, the lesion has affected the fibres between the posterior nerve roots and the sensory end organs, the fibres degenerate between the cut and the sensory end organs. (See Fig. 155.)

SECTION OF THE ANTERIOR ROOTS causes in the part supplied: (1) complete loss of tone in muscles; (2) complete paralysis of muscles; (3) temporary vaso-dilatation owing to cutting the white rami communicantes to the sympathetic system; (4) nutritional disturbances, *e.g.* disuse atrophy of muscles, &c. The muscles themselves will waste, unless measures be taken to prevent this. The degenerative changes will affect the nerve fibres between the cut and the muscles.

THE SPINAL MECHANISM OF CO-ORDINATED MOVEMENTS

The detailed study of the chief reflexes obtainable from a spinal animal has, in Sherrington's hands, yielded much information as to the linking

together of the various events which are concerned in the carrying out of every co-ordinated movement, and as to the conditions which determine the sequence and extent of the activities involved.

We may take, as the type of such a reflex, the flexion of the leg and thigh which ensues on the application of a painful stimulus to the ball of the foot, such as pricking with a needle or the application of the faradic current. Of course, in the spinal animal no pain can result from stimulation of any part below the level of section of the cord, and it is better, therefore, under such circumstances to speak of nocuous or pathic stimuli, since all stimuli which cause pain are such that, if their operation continued, they would result in damage to the material structure of the animal. This flexor reflex is also easily obtainable in the frog as a result of stimulating one of its toes by mechanical or chemical stimuli, but it is easier in the larger animal to analyse the different events involved in the reaction.

The effect varies with the strength of the stimulus. The minimal effective stimulus causes simply movement of the foot. As its strength is increased, this movement is attended by flexion of the leg on the thigh, and finally by flexion of the thigh on the body. With still stronger stimulus there is a spread to the opposite hind limb, which, however, performs the opposite movement of extension. Increase in the strength of stimulus causes not only an increase in the strength of contraction of the reacting muscles, but also an irradiation of the reaction to more and more muscles, or groups of muscles. The spread occurs always in definite order. The stimulus when represented by the prick of a needle can affect only one or two nerve fibres. The impulse carried along these fibres through a posterior root to the cord spreads in the cord, affects the motor neurones of the anterior horns, and causes them to discharge. The first discharge is, as a rule, limited to those in the immediate proximity of the entering impulses, but, even when minimal, involves the simultaneous action of more than one anterior root. We may say that the motor response is determined to a certain extent by the spatial proximity of the afferent to the efferent tracts, but that it is always plurisegmental, the most important determining factor being the adaptation of the movement to the stimulus which is applied.

The gradual spread of the response with increasing strength of stimulus is spoken of as '*irradiation*.' The nature of the response is determined by the *locus* or place of application of the stimulus and by the quality of the latter. While a painful stimulus causes flexion of the leg, deep pressure on the plantar surface of the paw causes extension—the '*stepping*' reflex. However extensive the irradiation, the muscles which are set into action are always such that their actions co-operate towards a given end. Thus, when the impulse spreads to the opposite limb and produces an extension, the reaction is such as would ensue when the dog steps on a sharp point and immediately retracts the irritated limb away from the injurious agent, while it extends the other limb in the first act of progression or movement away from the dangerous spot.

A superficial study of this reflex would therefore lead us to the conclusion that, by the varying resistance in the different synapses on the course of the connections of the stimulated afferent nerves, the impulses are directed so as to affect solely and exclusively the muscles whose activity will co-operate in the primary reflex. Such a description, however, would represent only one half of the process. Every muscle in the body is in a state of tone varying with its extension. If this tone is not to interfere with the carrying out of a reflex movement, there must be some means by which it can be inhibited. Such an inhibition occurs as the result of contraction of

antagonistic muscles; but the remarkable fact has been brought out by Sherrington that the impulses, which start on the surface of the body and set loose a chain of motor impulses resulting in the co-ordinated contraction of certain muscles, spread at the same time to the motor mechanisms governing

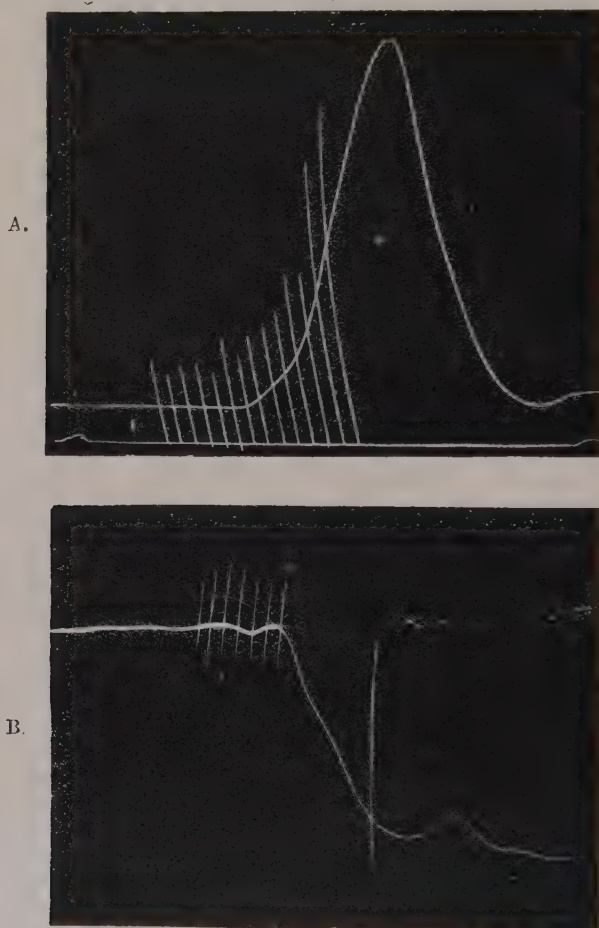


FIG. 156, A and B. (SHERRINGTON.)

The Flexion Reflex observed as Reflex Contraction (Excitation) of the Flexor Muscles of the Knee (A), and as Reflex Relaxation (Inhibition) of the Extensor Muscle (B).

The stimulus was a series of weak break induction shocks applied to a twig of the internal saphenous nerve below the knee. Observation B was made four minutes after A. Note the summation of stimuli, in each case six stimuli being required before the reaction was evoked.

the muscles antagonistic to the movement, and exercise on these an inhibitory effect.

This inhibition can be easily shown in a spinal animal in the following way. The anterior thigh muscles are cut away from their attachments to the tibia, and the patellar tendon is connected by a thread with a recording lever. On then exciting the flexor reflex by nocuous stimulation of the foot, the lever attached to the patellar tendon falls (Fig. 156), showing that the

extensor muscles have undergone actual elongation. The same effect is observed even when the hamstrings, the flexors of the knee, have been divided. The inhibition of the extensor tone is thus not only determined by the increased tension of the flexors, but is a direct result of the primary cutaneous stimulus.

From a broad standpoint, the function of the nervous system is the co-ordination of all the activities of the body so that these may be combined to one common end, viz. the preservation of the organism. For this purpose there must be no clashing between opposing activities of different parts. If one part is engaged in any action, this action must be the policy of the body as a whole. Yet the surface of the body is being continually played upon by ever-changing stimuli, tending to excite first one reflex and then another, and the activities so excited would produce confusion in the conduct of the animal, if there were not some means by which at any one time only one reaction should be in the act of being carried out. The imperative stimulus should dominate the actions of the body as a whole. Just as, in the mental world, attention must be undivided if we are to avoid confusion of judgment, so in the lower nervous activities there must always be concentration on one act or another. There may be a struggle of different stimuli, but one must finally be *prepotent* and annul altogether the influence of the others. The study of the spinal animal shows that this concentration of energy is obtained by the process of inhibition. Every successful reflex, *i.e.* one which actually occurs, inhibits all other reflexes which are not co-operative with the one which is taking place. We may, for instance, stimulate the area of skin which gives rise to the scratch reflex, and at the same time apply a painful stimulus to the foot. The result is not a movement compounded of the two reflexes, but as a rule the flexor reflex preponderates. If, for example, the scratch reflex be proceeding and then the foot be pricked, the scratch reflex immediately comes to an end, and the flexor reflex occurs. When this in its turn stops, the scratch reflex may be once more resumed (Fig. 157).

One stimulus may reinforce another if the reactions ensuing on the two stimuli are allied—*i.e.* tend to co-operate one with another. In every other case, however, an afferent impulse entering the cord and spreading to a motor mechanism, so as to produce a co-ordinate contraction of various muscles, causes at the same time inhibition of the muscles antagonistic to the movement, and a block or inhibition in all other reflex arcs of the cord.

The anatomical basis of the various events involved in the carrying out of such a reflex as that just studied is shown in the diagram (Fig. 158). In this diagram the nerve fibre α represents the pain-receiving or nociceptive nerve from the skin of the foot. This passes by a posterior root into the spinal



FIG. 157. Scratch Reflex temporarily inhibited by Application of a Pathic Stimulus to Foot.

Signal A, stimulation of scratch area. Signal B, stimulation of paw by strong induction shock.

cord, where it divides and gives off a number of collaterals. These collaterals, as we have already seen, pass in various directions; some to the neighbouring grey matter, some to the centres in the higher parts of the nervous system. Neglecting the latter and any intermediate neurone which may be intercalated between the afferent fibre and the motor cell, we see that those collaterals which affect the motor cells of the muscles of the two hind limbs can be divided into two sets, one of which always produces during activity excitation in certain efferent neurones, whilst the other produces inhibition of the efferent neurones of the antagonistic muscles. The single afferent nerve fibre is, therefore, with regard to one set of its central terminal branches, specifically excitator and, in regard to another set of its central endings, specifically

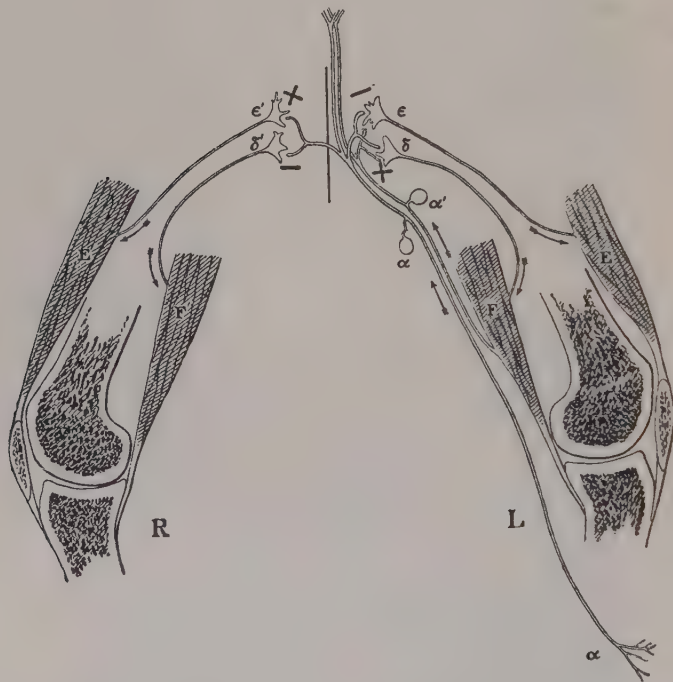


FIG. 158. Diagram indicating Connections and Actions of two Afferent Spinal Root Cells α and α' in regard to their reflex influence on the extensor and flexor muscles of the two knees. The sign + indicates an excitatory effect, the sign - an inhibitory effect. (SHERRINGTON.)

inhibitor. In the case in point the central terminal branches of the nerve α are excitator for the flexor muscles of the same side, and inhibitor for the extensor muscles of the same side and for the flexor muscles of the opposite side.

The ascending branches of the nerve fibre in the same way will have endings which, while inhibitor for the greater number of other possible reflex changes, will be excitator in a slight degree for certain efferent neurones whose action is allied to that of the primary reflex. The diagram shows also that the contraction of the flexor muscle, set up as the result of stimulating α , itself initiates a secondary reflex process from muscle up the nerve fibre α' and back again to the muscle by the efferent neurone. This muscular afferent nerve also has central terminations of two signs—excitator to itself and inhibitor to the antagonistic muscles. For the sake of clearness the

diagram omits a number of other channels coming from other regions of the cord or from other efferent nerves, the sign of which would be negative, *i.e.* which would tend to inhibit the activity of the whole reflex arc.

We see that from every sensitive point on the surface of the body impulses can be initiated which will set into action many chains of neurones, and will have a widespread influence throughout the central nervous system. It is important to note that the efferent path innervating, say, the flexor muscles of one side is common to many reflexes. It is used, for instance, by mutually antagonistic reflexes such as the 'scratch reflex' and the 'flexor' or 'pain reflex.' We must assume that the mutual inhibition of different reflexes occurs, not in the '*final common path*'—*i.e.* in the motor neurones which must always remain open—but further back in the arc, probably near its afferent side.

We have reason to believe that the propagation of impulses through the central nervous system involves expenditure of energy, and that the seat of greatest expenditure may be located at the synapses. It follows that the result of any particular sensory stimulation will not be absolutely invariable, but that the spread of the nerve process in the nervous system, and the degree of block presented by the various synapses and determining the potency of any given reaction, will depend on the condition of the various synapses at the time of the stimulation.

This condition may be altered in various ways. Repeated excitation causes in the synapses, just as in the sensory and motor nerve-endings, a condition of fatigue. Stimulation confined to a single point in the 'scratch area' of the spinal dog excites a scratch reflex which rapidly dies away. On shifting the exciting electrodes a little to one side, the reflex act begins again, often with greater force than at first; and a very prolonged reaction can be induced by gradually moving the electrodes along the surface of the skin. A reflex arc rapidly shows signs of fatigue, and the minute change in locus of stimulus, which is required to reinduce a practically identical action, shows that the seat of fatigue must lie chiefly on the afferent side of the arc, perhaps in the sensory nerve-endings as well as in the first synapses through which the impulse has to pass. This easy incidence of fatigue tends to cut short any given reaction and to render it easier for other reactions to take its place.

Just as excitation causes fatigue and furnishes a hindrance to repetition of the same act, so the reverse process of inhibition, which is a large component of every reaction, is followed by a condition of increased excitability, or diminished resistance to the passage of impulses. In each case there is a tendency for a 'swing-back' to take place from inexcitability to over-excitability, from excitation to inexcitability. This "*successive spinal induction*," as it has been termed, may be seen on inhibiting some movement by the excitation of an independent reflex. Thus the scratch reflex is excited and then, while the excitation is still continued, the reaction is inhibited by excitation of the extensor or stepping reflex. As soon as the stepping reflex has passed off, the scratch reflex returns with an intensity greater than before. This successive spinal induction explains the tendency which exists in the spinal cord to an alternation of response; every act tending to come to an end by fatigue and, as a result of negative spinal induction, inducing the opposed or antagonistic act. Thus if a spinal dog be held up in the vertical position, so that the hind limbs hang freely, these latter execute a series of alternate movements of flexion and extension. The starting-point of these is the stretching of the anterior thigh muscles. Once started they

continue of themselves, each act exciting the alternating antagonistic act. (Fig. 159.)

A reflex act has often been distinguished from other reactions, described as conscious or purposive, by its fatality—*i.e.* by the invariability with which it results on a given stimulus, whether the reaction be for the good of the animal as a whole or not. Thus a decapitated eel will wind itself with equal readiness around a stick or a hot poker. *All* reactions are, however, purposive. The machinery for them has been evolved, and the paths laid down in the spinal cord, under the action of natural selection, so that they must act, at any rate *in the average of cases*, towards the well-being of the animal as a whole. Since the nerve path involved in any reaction includes a number of synapses, each of which may be influenced from other parts of the body in a positive or negative direction, an absolute uniformity of response cannot be

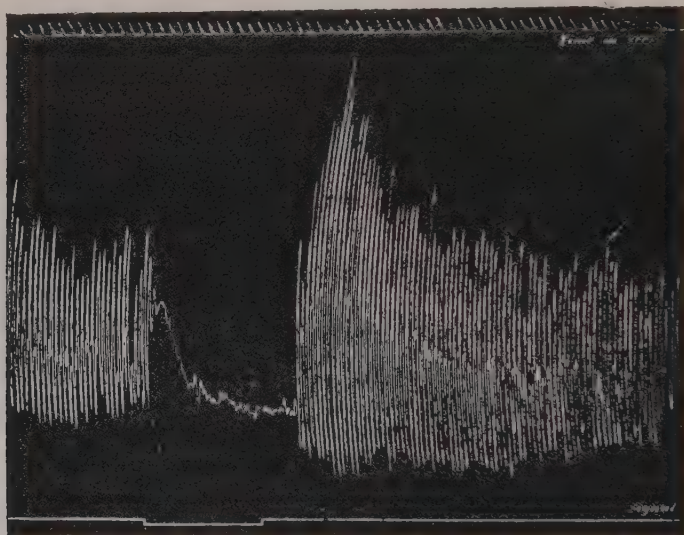


FIG. 159. 'Mark-time' Reflex in Spinal Dog, inhibited by slight Stimulation of the Tail (duration of stimulation shown by signal). Note the augmentation of the mark-time reflex following the inhibition (*successive spinal induction*). (SHERRINGTON.)

predicated for any one reaction. There will be changes in the facility with which it is evoked and changes in its extent, and these will become the more operative the greater the complexity of the arc and the larger the number of other impulses to which it may be subject. The fatality of response is therefore shown only at its best in the very simplest of reflexes, or in the most lowly organised nervous systems.

The purposive character of the reflexes obtained from the spinal frog has sometimes led writers, especially in pre-Darwinian days, to endow the spinal cord with a guiding intelligence. At the present time we recognise that every reaction of a living being must be purposive, in the sense of being adapted to the preservation of the species if the latter is to survive in the struggle for existence. The question as to whether we are justified in predicating the existence of even a germ of consciousness or volition in the spinal animal must be decided in the negative. "Associative memory would seem to be a postulate for the very existence of perception. Where even simplest ideas are not, there cannot be consciousness. Animal movements that are appro-

priate not only for an immediate but also for a remote end indicate associative memory. The approach of a dog in answer to the calling of its name, the return of an animal when hungry to the place where it has been wont to receive food, such movements may be taken as indicative of consciousness since they indicate the working of associative memory. Examined by this criterion all purely spinal reactions fail to evince features of consciousness." (Sherrington.)

THE PART PLAYED BY AFFERENT IMPRESSIONS IN THE CO-ORDINATION OF MUSCULAR MOVEMENTS. Every reflex act is initiated in the first place by some form of sensory stimulus. In the carrying out of the muscular contractions and the resultant movements of the limbs, other impulses are set up in the structures which subserve deep sensibility, including those of muscles. These secondary afferent impulses in their turn affect the excitability and the activity of the motor neurones, and are important whether the movements be aroused by immediate sensory stimulation of the surface of the body, or through the higher parts of the brain, as in volitional movements.

Their significance is shown by the marked disorders of movement produced in a limb by section of some or all of its afferent nerves. Thus if all the posterior roots supplying one hind limb of the frog be divided, the posture of the desensitised limb is abnormal, whether the frog be suspended or be in a sitting posture. Such a frog generally swims with the desensitised limb in permanent extension. The complete absence of muscular tone under these circumstances has already been mentioned. When a contraction of the quadriceps extensor is induced by a single shock applied to the intact ant. crural nerve, the curve obtained shows a relaxation line much slower and more prolonged than when the cut nerve is similarly excited. In the latter case, or when the posterior roots alone are divided, the lever at the end of relaxation dips below the base line with an inertia fling, which is never present when the nerve is intact. The contraction of the muscle, when its afferent path is intact, seems to develop reflexly in the muscle itself a condition of tone which damps the inertia swing of the contraction. In the dog, after section of the afferent nerves of one hind limb, this limb is not at first used for walking; it is kept more or less flexed at hip and knee, and later, when it is employed in walking, it is lifted too high with each step. After division of the afferent fibres of both limbs, these appear as if they were affected with motor paralysis. At first during walking, the fore limbs simply drag the hind limbs after them, though later, as the hind limbs are drawn along, they make alternate movements and may ultimately afford a certain amount of support to the body.

Still more striking effects are observed in complete anæsthesia of the fore limb in monkey or man. The limb is permanently paralysed; it is never used in climbing nor in the taking of food. That the peripheral motor mechanism is intact is shown by the fact that stimulation of the appropriate area of the cerebral cortex in such animals elicits at once a perfectly normal movement of the hand or limb. It seems, however, impossible for the cortex to *initiate* such movements in the absence of all afferent impulses arriving from the limb. Similar paralysis was observed by Chas. Bell in the upper lip of the ass after section of the corresponding branches of both fifth nerves, and was interpreted by him as indicating a possible motor function for these nerves.

In these phenomena of sensory paralysis we are dealing with the effects produced by the deprivation of two distinct classes of afferent impressions, viz. those from the skin and those from the deep structures and muscles.

The phenomena due to these two factors may be studied separately. If in the monkey all the afferent brachial roots except the last cervical, which supplies cutaneous sensations to the whole hand, be divided, the monkey uses the arm and hand both in climbing and in taking food. A marked ataxy of the movement is, however, observed. Whereas the normal monkey, in taking grains of rice out of the observer's hand, exhibits perfect precision of movement so that he rarely touches the hand on which the grains are lying, the monkey with only cutaneous sensibility remaining grasps clumsily with the whole hand, and the arm sways as it is put out, often missing the object aimed at altogether. Cutaneous insensibility of the hind limb causes very little disturbance of locomotion, the alternate movements of which seem to be started by the stretching of the structures at the front of the thigh. On the other hand, a patient affected with such a loss (*e.g.* in *tabes dorsalis*) may be the subject of 'static ataxy,' *i.e.* he is unable to stand with his feet together and his eyes shut. The afferent impressions from the skin of the feet appear therefore to be necessary for the maintenance of static equilibrium.

In the carrying out of co-ordinated movements, such as those of locomotion, the impressions from the muscles play a more important part. Division of the afferent nerves from the muscles gives rise to a condition of tonelessness, and the passive mobility of the joints is greater than usual, so that the hip with the limb extended at the knee may be flexed to an abnormal extent. The effect of this loss of tone is more apparent in the case of certain muscles. The disturbance of co-ordination resulting from the cutting off of afferent muscular impressions is well seen in cases of *tabes dorsalis* (locomotor ataxy) in man, and to a slighter extent in cases of peripheral neuritis affecting chiefly the sensory nerves of muscles. The ataxic gait of such a patient is characteristic. There is no loss of power in the muscles, but there is loss of control. The patient is unaware of the position of his limbs and has to guide his walk by visual impressions: even then the movements are inco-ordinated. The contraction of every muscle is exaggerated, so that in walking the leg is first raised too high and then is brought down on to the ground with a stamp. As the disease progresses the loss of control becomes more and more pronounced, so that attempts to walk simply give rise to a profusion of disordered movements, the legs being thrown in all directions with the patient's efforts, but with no effective result. The centres are no longer informed of the degree to which each muscle is contracted, and the impressions are wanting which should cut short the contraction of a muscle when it has attained its optimum and which should inhibit the antagonists during the contraction and induce activity of the antagonists in successive alternation to those of the other muscles. In such a patient, therefore, walking finally becomes impossible, and, with well-nourished muscles and a motor path which is intact, he is condemned to pass the rest of his days in bed.

THE EFFECT OF POISONS ON THE SPINAL CORD

The reflex functions of the spinal cord may be abolished by the same drugs, such as ether, chloral, &c., which abolish conductivity in a nerve fibre. The central effect of these drugs is obtained with much smaller concentrations than is the case with the peripheral nerves. Hence their value as general anæsthetics.

More interesting from the point of view of the physiologist is the action of such a drug as strychnine, or the somewhat similar action of the toxin formed by the tetanus bacillus. If a small dose of strychnine be injected into a spinal frog, after a short period of heightened irritability the slightest

stimulus applied to the surface will cause spasms, which may affect every muscle in the body. Pinching the foot, instead of causing it to be drawn up, now causes the legs, arms and back to be rigidly extended. The extension is not a co-ordinated act, but is associated with strong contraction of the flexors, the final position of the limbs being determined by the preponderating strength of the extensor muscles. The real meaning of this condition is seen if, in a spinal mammal, the extensor muscles be connected with a lever and the flexor muscles cut. On exciting the flexor reflex by pricking the foot, there is instantaneous relaxation of the extensor muscles. A small dose of strychnine is now given, insufficient to cause general convulsions. It is then found that on pricking the foot the extensor muscles respond, not with inhibition but with a contraction. Strychnine abolishes the inhibitory side of every co-ordinated act, so that it appears to convert the process of inhibition into one of excitation. Co-ordination, therefore, becomes an impossibility, and stimulation of any spot excites contractions not only of the appropriate muscles but also of the antagonists of these muscles, the direction of the resulting movement being determined simply by the relative strength of the two sets of muscles.

The same effect is produced by tetanus toxin, and, since the action of this toxin may be confined in its early stages to one limb, it is possible to show the abolition of the inhibitor side of the reflexes in this one limb while the limb of the other side reacts normally to the stimulus. The same abolition of inhibition is found whether the response be excited by stimulation of the skin or by voluntary excitation from the cortex of the brain. It is impossible for a patient under these circumstances to open his mouth because every willed impulse for opening innervates at the same time the stronger masseter muscles and effectively closes the mouth.

TROPIC FUNCTIONS OF THE CORD. The reflexes which are excited by painful or noxious stimuli must be regarded as prepotent in that their inhibitory effect on other reflexes is more marked than that produced by any other quality of stimulus. In the struggle for existence the reaction to noxious stimuli must predominate over those due to any other kind, since it is essential for the survival of the animal that the stimulus should be removed or avoided, so that the animal should escape from its injurious effects.

It is natural, therefore, that after complete section of the afferent nerves from any part of the surface of the body, there should be a tendency to trophic disturbances such as the formation of ulcers, &c. Such ulceration is frequently observed in patients suffering from spinal disease. After section of the first division of the fifth nerve ulceration of the cornea is often produced. These effects are, however, due to the absence of the normal protective reactions of the part, and can be prevented by scrupulous cleanliness and protection of the anæsthetic part from all possible injuries. There are other trophic effects caused by nerve lesions which cannot be ascribed to the mere absence of protective reflexes. Thus inflammation of the posterior root ganglia often sets up 'herpes zoster,' or 'shingles,' in the region of cutaneous distribution of the corresponding sensory nerve. Changes in the skin ('glossy skin'), nails and hair are often seen after irritative injuries of nerves to the part. Section of a motor nerve causes rapid changes in the skeletal muscles supplied, which become smaller and after months or years may disappear altogether, being replaced by connective tissue. The changes in the excitability of the muscles produced under these circumstances have already been described.

It seems that the nutrition of a tissue is determined by its activity, and

this in turn is under the control of some nerve path. Section of the nerve path, by cutting away the impulses which normally maintain the activity of the part, must at the same time seriously affect its nutrition. Thus the muscles which, though striated, are not so immediately under the control of the central nervous system, such as the sphincter ani, do not undergo degeneration after section of their nerves or after extirpation of the lower part of the spinal cord.

On the other hand, it is only during post-foetal life that the activity of the skeletal muscles is determined by the motor nerves of the cord. Thus they may be developed normally even in the complete absence of a central nervous system. Whether we are justified in assuming the existence of trophic nerves exercising an influence on the nutrition of the part they supply, apart from any influence on its other functions, the experimental evidence before us is not sufficient to decide ; nor can we as yet give a physiological analysis of the changes in nutrition which may be brought about in hysterical patients under the influence of emotion.

CHAPTER XVII

THE BRAIN STEM

In examining successive sections from the spinal cord up through the medulla, the first change which makes its appearance is due to the decussation of the pyramids. Throughout the spinal cord, fibres have been crossing from one side to the other through the anterior white commissure, many of them belonging to the pyramidal system. But at the lower border of the medulla we see a large mass of fibres crossing between the anterior columns and the postero-lateral columns, at first cutting off the head of the anterior horn and later on breaking this up altogether, so that the only definite collection of grey matter left in this situation is a small part of the lateral column of grey matter known as the lateral nucleus. In this way are formed the big anterior columns of the medulla, which are known as the pyramids and contain all the fibres that in the cord are represented by the direct and crossed pyramidal tracts.

The next change is due to the ending of the posterior columns (Fig. 160). These are the central ascending branches of dorsal nerve roots, having, therefore, an origin outside

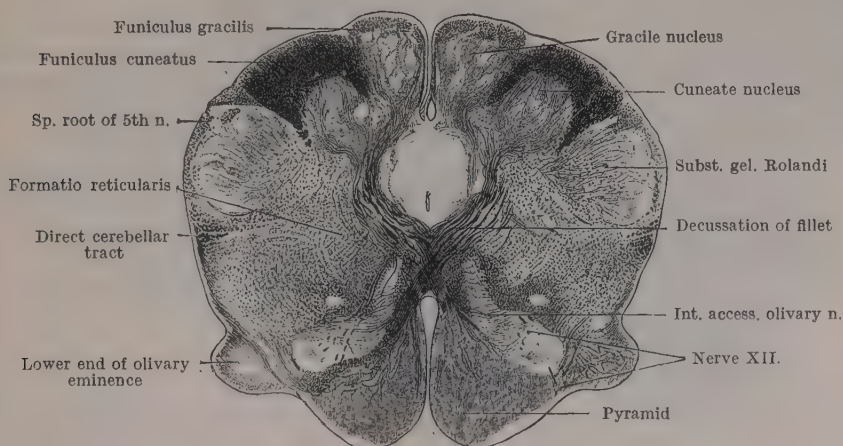


FIG. 160. Transverse section through Medulla of Fœtus, immediately above
Pyramidal Decussation. (CUNNINGHAM.)
Stained by Weigert-Pal method.

the cord. On their way up the cord they send in collaterals to end in the grey matter of the posterior horn. The main mass terminates in the medulla, just above the pyramidal decussation, in two collections of grey matter—the *nucleus gracilis* and the *nucleus cuneatus*—which are formed by a great hypertrophy of the grey matter at the root of the posterior horn. The effect of this development in the dorsal region of the medulla is to push the head of the posterior horn outwards. At the same time this mass becomes enlarged, so that in section we have three grey masses from within outwards, the nucleus gracilis, the nucleus cuneatus, and the nucleus (or substantia gelatinosa) of Rolando.

The fibres of the postero-median column (of Goll), which are derived chiefly from the lower limb, end in arborisations round the cells of the nucleus gracilis, while those of the postero-external column or column of Burdach, of which the majority is formed by fibres from the upper limbs, terminate in the grey matter of the nucleus cuneatus. The cells of these two masses of grey matter of course give off axons, which can carry on the impulses brought to them by the fibres of the posterior columns. These axons speedily

leave the dorsal aspect of the medulla, bending round, as the *arcuate fibres*, to the deeper parts of its structure. Thus nothing is left to take the place of the posterior columns on the posterior aspect of the cord. With the disappearance of these columns and the development of the pyramids, we get a practical obliteration of the anterior fissure and a displacement of the central canal towards the dorsal surface.

A little higher up (Fig. 161) the canal opens out altogether, forming the fourth ventricle, covered on its dorsal surface only by a thin layer of ependyma, a simple epithelium representing all that is left of the dorsal wall of the primitive cerebral vesicle. The appearance of the section is now modified by two structures. In the first place, a new mass of grey matter, consisting of a thin layer shaped like a flask with its orifice directed inwards, is developed in the lateral part of the medulla, between the pyramids in front and the tubercle of Rolando behind. This is the *olivary body*, and it has on its inner and dorsal sides two little grey masses which are the *accessory olivary bodies*. The other feature is the new relay of sensory fibres

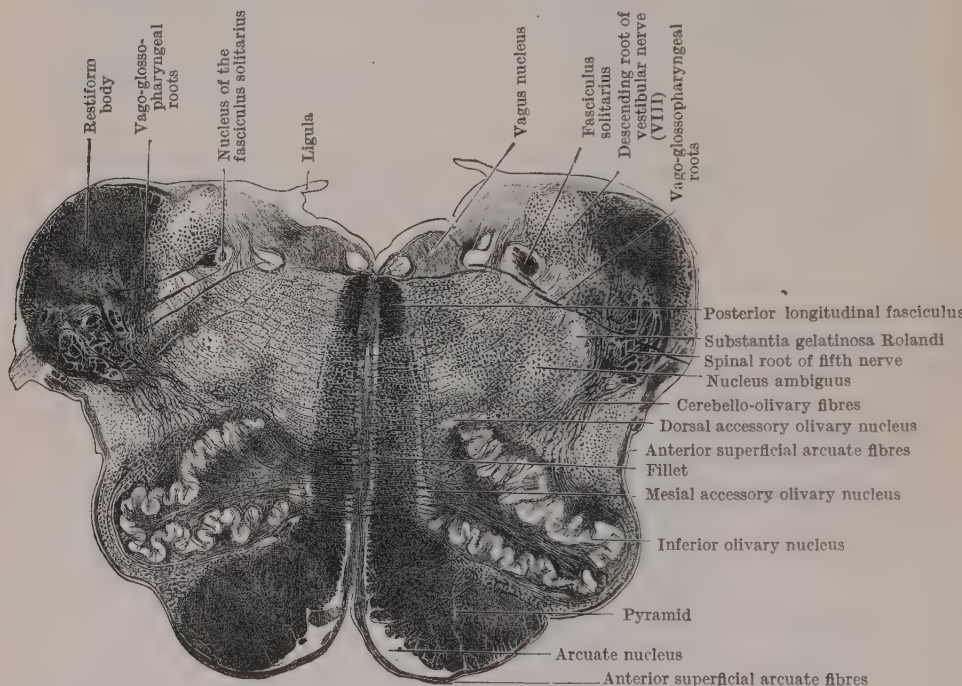


FIG. 161. Transverse section through the middle of the Olivary Region of the Human Medulla. (CUNNINGHAM.)

which start from the dorsal nuclei, the nuclei gracilis and cuneatus. These fibres run outwards and forwards from the nuclei right round the medulla. Some fibres pass into the restiform body of the same side; a larger number, forming the superficial arcuate fibres, pass superficially to the olive to join the restiform body of the opposite side, while others, the deep arcuate fibres, pass behind the olives, and crossing in the median raphe turn upwards in the broken mass of grey and white matter which lies between the olives and the superficial grey matter of the fourth ventricle. This decussation, which is known as the 'decussation of the fillet' or the 'sensory decussation,' takes place immediately above the level of the decussation of the pyramids. In its upward course it forms a conspicuous strand of fibres, lying close to the mesial plane and separated from its fellow of the opposite side simply by the median raphe. To this collection of fibres is given the name of the *mesial fillet* or *lemniscus*. It is perhaps the most important of the afferent tracts of the brain stem, receiving as it does continuations of the posterior columns of the cord as well as contributions from the various sensory cranial nerves. It may be traced forwards as far as the thalamus and subthalamic region, where its fibres terminate. The region corresponding to the anterior column of the spinal cord is thus invaded in the medulla by two great longitudinal tracts of

fibres, the pyramids and the tracts of the fillet. The region corresponding to the anterior basis bundle, *i.e.* that part of the anterior columns occupied chiefly by intra-spinal fibres, is thus pushed further backwards and finally comes to lie immediately beneath the grey matter of the floor of the fourth ventricle. Immediately dorsally to the fillet is to be seen another well-marked bundle of longitudinal fibres, known as the posterior longitudinal bundle. Its fibres, which serve to connect the nuclei of many of the cranial nerves, can be regarded as analogous to the constituent fibres of the anterior basis bundle in the cord, and can in fact be traced into this part of the anterior columns in the first and second cervical segments of the cord.

The fourth ventricle is covered in by the cerebellum, which is attached to the axial part of the brain by three peduncles, the inferior peduncles or restiform bodies, the lateral peduncles, which form the great mass of transverse fibres known as the pons

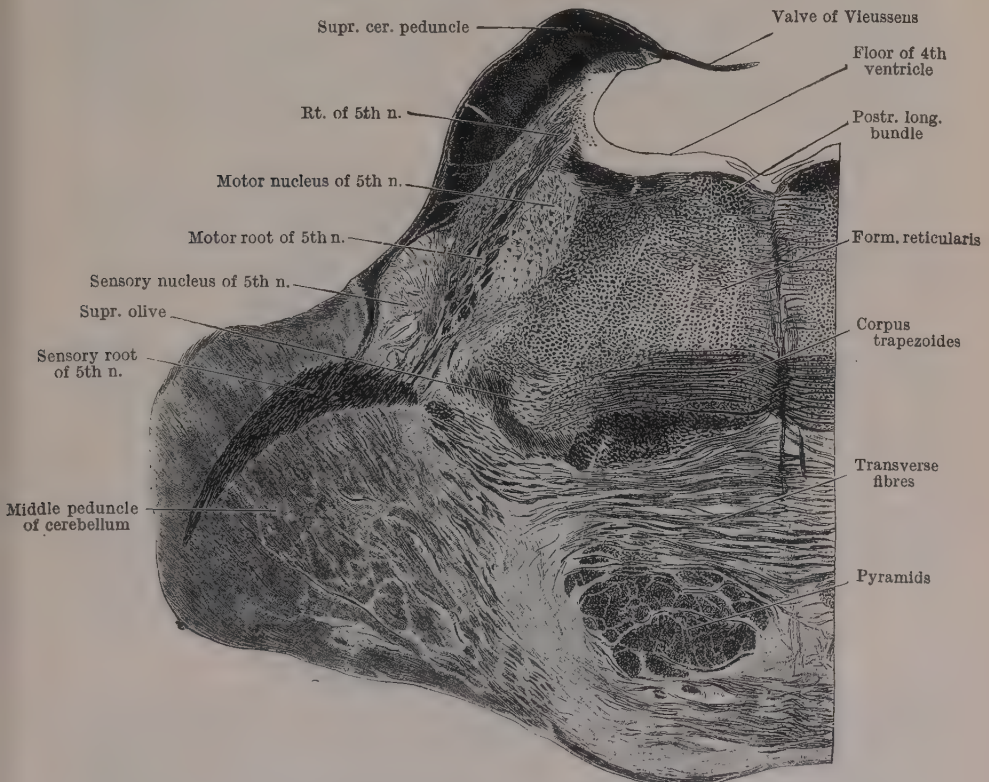


FIG. 162. Transverse section through middle of Pons Varolii of Orang on level of Nuclei of Fifth Nerve. (CUNNINGHAM.)

Varolii, and the superior peduncles, which run forward to the posterior corpora quadrigemina. The restiform bodies can be regarded as the direct continuation forwards of the lateral columns of the cord, *minus* the pyramidal tracts, the chief remaining tract therefore being the dorsal or direct cerebellar tract. In the region of the dorsal nuclei, however, it receives accession of fibres from the gracile and cuneate nuclei of the same side and, through the superficial arcuate fibres, from the nuclei of the opposite side, and thus passes as a thick white bundle into the cerebellum. Among these arcuate fibres are also a number derived from the olivary body of the opposite side, known as the olivo-cerebellar fibres. On its way it is joined by a smaller bundle, the internal restiform body, which conveys fibres from the vestibular division of the eighth nerve and also serves to connect Deiters' nucleus with the cerebellum. The restiform body is thus made up of the following fibres:

(1) The direct or dorsal cerebellar tract, derived from the cells of Clarke's column on the same side of the cord.

(2) The posterior superficial arcuate fibres, derived from the gracile and cuneate nuclei of the same side.

(3) The anterior superficial arcuate fibres, from the gracile and cuneate nuclei of the opposite side.

(4) The olivo-cerebellar fibres.

(5) The vestibulo-cerebellar fibres.

A section through the pons shows the fourth ventricle widely dilated, with a floor formed of grey matter as in the medulla. The chief difference in the appearance of the section is due to the great masses of transverse fibres which pass into the pons by the lateral peduncles of the cerebellum, cross by the median raphe, and turn either upwards or downwards on the opposite side or end in connection with the nerve cells which are scattered throughout the white fibres. The pyramids can still be seen as thick longitudinal bundles on each side in the midst of the transverse fibres. They are considerably larger than in the medulla, and become still larger as we trace them up towards the mid-brain, owing to the presence of a number of fibres which are derived from the cortex cerebri and end in the grey matter of the pons. The tract of the mesial fillet lies on each side of the middle line dorsally to the transverse fibres. A little to the outside of the fillet is seen a special mass of grey matter, known as the *superior olive*. The nervous mass lying behind the transverse fibres of the pons, between them and the grey matter of the floor

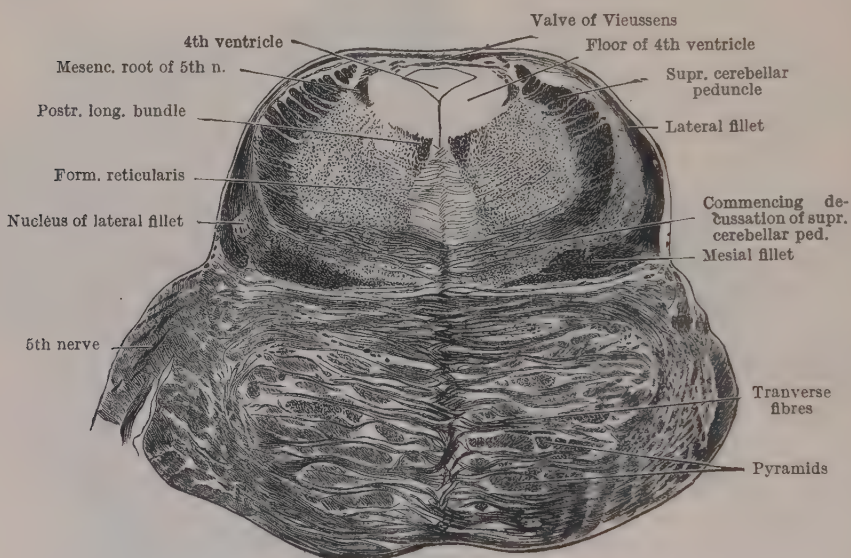


FIG. 163. Section across upper part of Pons Varolii of the Orang. (CUNNINGHAM.)

of the fourth ventricle, is known as the *formatio reticularis*. It is divided into a lateral and mesial part by the fibres of the hypoglossal nerve. In the lateral portions there is a considerable quantity of grey matter, which can be regarded as continuous with the grey matter of the lateral horns of the cord. The 'lateral nucleus' is simply a condensed part of this grey matter, lying between the olive and the gelatinous substance of Rolando. The mesial part of the *formatio reticularis* is almost free of nerve cells. The reticular appearance of this part of the pons is due to the intersection of fibres which run longitudinally and transversely. The transverse fibres are a continuation of the deep arcuate fibres. The longitudinal fibres in the outer part of the *formatio reticularis* are the representatives of the lateral columns of the cord after the removal of the direct cerebellar and the crossed pyramidal tracts. They include therefore the antero-lateral ascending tract (tract of Gowers) and a number of other fibres corresponding to the lateral basis bundle in the cord. In the mesial part of the *formatio reticularis* the longitudinal tracts are the tract of the mesial fillet and the posterior longitudinal bundle on each side of the middle line. In the upper part of the pons Varolii a well-marked collection of transverse fibres is to be seen lying dorsally to the tracts of the mesial fillet. This collection is called the *corpus trapezoides* and is made up of ascending fibres derived from the nuclei of the cochlear or auditory part of the eighth nerve.

A little further forward a section will escape the cerebellum altogether, being bounded

ventrally by the upper or anterior part of the pons and dorsally by a thin mass of grey matter, the valve of Vieussens (Fig. 162). On each side of the valve of Vieussens may be seen the superior peduncles of the cerebellum. As these peduncles are traced upwards they sink gradually deeper into the pons until they lie on the outer side of the tegmental region or *formatio reticularis*. They are made up of fibres which run from the dentate nucleus of grey matter in the cerebellum to the mid-brain, where they decussate below the Sylvian iter and end in the red nucleus and in the thalamus of the opposite side. They also contain the continuation upwards of the antero-lateral ascending tract which, passing up in the superior peduncles, bends dorsally round the fourth nerve and then, turning backwards, ends in the superior vermis of the cerebellum. In a section through the upper part of the pons, the division into the *formatio reticularis* or *tegmentum* and the more ventral part made up of transverse and longitudinal fibres, the pedal portion, is well marked (v. Fig. 163). The fourth ventricle has now become constricted to a narrow canal triangular in section and closed above by the valve of Vieussens. It is surrounded, especially on its ventral side, by grey matter containing the cells of origin of the fourth nerve. In the tegmental portion we may distinguish on each side the superior cerebellar peduncle. Outside the longitudinal fibres of this peduncle are a number of transverse fibres derived from the *corpus trapezoides* seen in the previous section. To these fibres is given the name of the 'lateral fillet.' They are on their way to end in the roof of the mid-brain in the inferior corpora quadrigemina. The posterior longitudinal bundle lies near the middle line, immediately under the grey matter of the floor of the fourth ventricle, while the longitudinal fibres of the mesial fillet form a distinct mass in the ventral portion of the *formatio reticularis*. The pedal portion contains the longitudinal fibres of the pyramids, now much increased in amount, cut up into bundles by transverse fibres derived from the middle peduncles of the cerebellum.

The cerebellum, which covers in the fore part of the fourth ventricle, will be described in greater detail later on. At present it will suffice to say that it consists of a middle and two lateral lobes. The surface of the middle lobe turned towards the fourth ventricle is known as the inferior vermis, the dorsal surface forming the superior vermis. Each vermis and each lateral lobe is subdivided into a number of smaller lobes. The intimate structure of all parts of the cerebellum is however very uniform. It consists of a mass of white matter internally, covered by a layer of grey matter, the extent of grey matter being largely increased by the formation of numerous parallel and more or less curved grooves or sulci which give the whole organ a laminated appearance. In the mass of white matter, which forms the core of each lateral hemisphere, is an isolated nucleus of grey matter known as the *corpus dentatum*. In the white matter of the middle lobe is another mass of grey matter known as the roof nucleus or *nucleus fastigii*. Between the nucleus fastigii and the nucleus dentatum are, on each side, two other nuclei, the *nucleus globosus* and the *nucleus emboliformis*.

THE MID-BRAIN

A little further forward the fourth ventricle comes to an end, and the section passes through the mid-brain (Fig. 164), the cavity of the second cerebral vesicle being represented by the narrow Sylvian aqueduct, bounded dorsally by the corpora quadrigemina and ventrally by the crura, the stalks of the brain. The crura are divided by an irregular mass of grey matter, the *substantia nigra*, into two parts. The ventral portion is known as the *pes* or *crusta*. It is composed almost entirely of longitudinal white fibres, among which is the continuation forwards of the pyramids of the medulla. The pyramids, however, form only the middle two-fifths of the total mass of fibres, the rest consisting of fibres which run from the different parts of the cerebral cortex, especially from the frontal and temporal lobes, to end in the *formatio reticularis* of the pons, probably in relation with the grey matter in this situation and with the endings of the transverse fibres derived from the cerebellum and forming its middle peduncles. The dorsal part, the *tegmentum*, is a direct prolongation forwards of the *formatio reticularis* of the medulla and pons, and, like this, contains much scattered grey matter.

On a level with the inferior corpora quadrigemina a number of decussating fibres are to be seen in the tegmentum, which are derived from the superior cerebellar peduncles. Their decussation is complete at the level of the upper border of the inferior corpora quadrigemina. Here each peduncle turns upwards, and a large proportion of its fibres end in the *red nucleus* (Fig. 165), a mass of grey matter forming a conspicuous feature of sections through the anterior part of the mid-brain. Many of the fibres pass round the red nucleus, forming a sort of capsule over it, to the ventral part of the optic thalamus, in which they probably end. It is possible that a certain proportion pass through the optic thalamus and run straight to the cerebral cortex of the Rolandic area. The lateral

fillet has disappeared from the region of the tegmentum and passed into the inferior corpora quadrigemina. The mesial fillet forms a flat band lying to the outer side of the red nucleus and comes into close relation with a ganglion of the fore-brain, known as the *internal geniculate body*. The roof of the mid-brain is formed by the corpora quadrigemina. The inferior corpora quadrigemina are composed of central grey matter encapsulated by white matter, derived chiefly from the lateral fillet, and therefore ultimately from the auditory nerves. The superior corpora quadrigemina are composed of several layers of grey matter traversed by nerve fibres, derived partly from the mesial fillet, partly from the optic tract, and partly from the occipital lobe of the cerebral hemisphere.

THE AXIAL GREY MATTER

In the spinal cord we could distinguish between the anterior grey matter giving origin to the motor nerves, the posterior grey matter serving as an end station for a

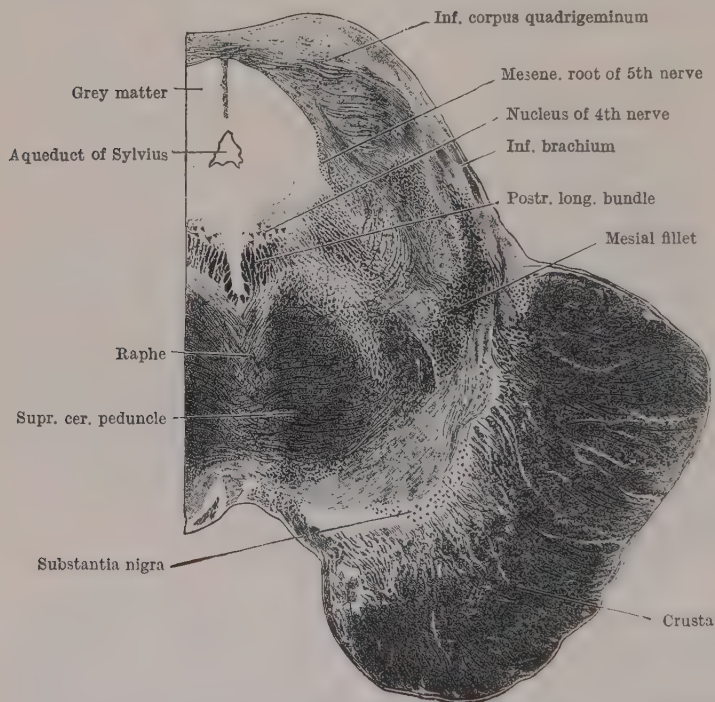


FIG. 164. Transverse section through Human Mid-brain, on level of the Inferior Corpora Quadrigemina. (CUNNINGHAM.)

number of the sensory posterior root fibres, and a lateral horn, less well marked, probably giving origin to the visceral system of nerves. As the central canal widens out to form the fourth ventricle, the relative position of these various parts becomes altered, the anterior grey matter being now nearest the median line, while the posterior grey matter lies more laterally. Part of the lateral grey matter is displaced deeper than the rest, from which it is separated by the tangle of fibres and cells known as the *formatio reticularis*. All the cranial nerves from the third to the twelfth arise or end in the axial grey matter, or in close proximity to it. So great however is the complexity of this part of the nervous system, and so involved are the genetic relations of the various nerves, that it is difficult or impossible in many cases to state definitely the spinal analogies of these nerves.

The cranial nuclei (of origin or termination) may be roughly classed as follows:

(1) *Somatic Motor Nuclei*. These consist of an almost continuous column of multipolar cells, lying close to the middle line on each side in the floor of the fourth ventricle,

the Sylvian iter, and the back part of the third ventricle. From below upwards these groups of cells give origin to the fibres of :

- (a) The hypoglossal nerve (Figs. 166, 167).
- (b) The sixth nerve.
- (c) The fourth nerve.
- (d) The third or oculo-motor nerve.

(2) *Splanchnic Sensory Nuclei*. Immediately outside the column of motor cells is a column of grey matter which receives the terminations of the afferent fibres belonging to the ninth, tenth and eleventh nerves, and is sometimes called the vago-glossopharyngeal-accessory nucleus. This grey matter, of course, does not give rise to the fibres of

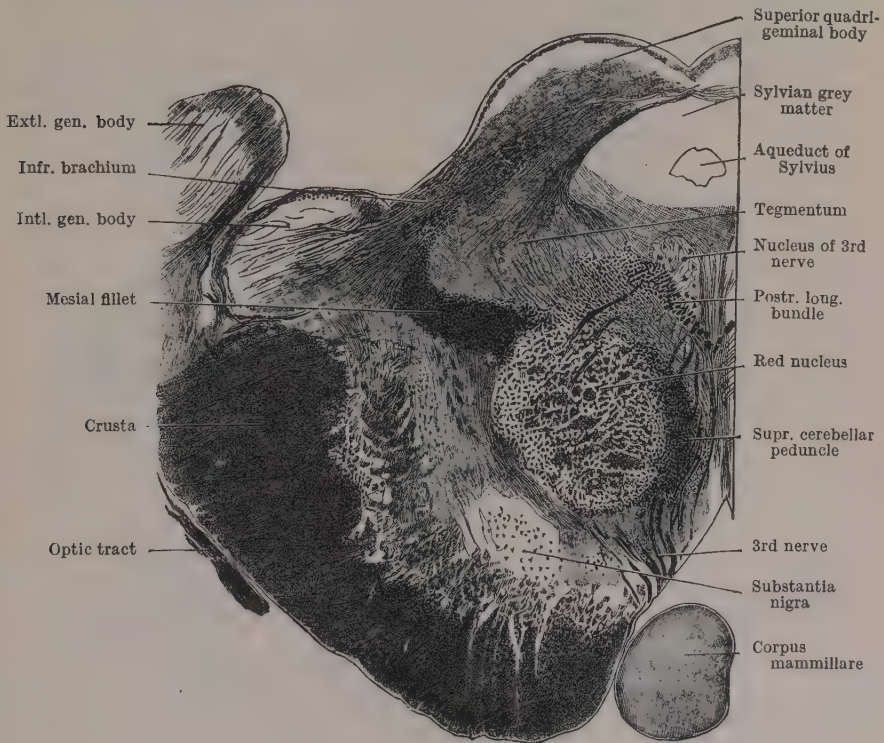


FIG. 165. Transverse section through Human Mid-brain at the level of the Superior Corpus Quadrigeminum. (CUNNINGHAM.)

these nerves which, like other sensory nerves, are axons of ganglion cells lying outside the central nervous system (Figs. 166, 167).

(3) *Splanchnic Motor Nuclei*. These lie more deeply at some distance from the middle line, and include the *nucleus ambiguus* for the efferent fibres of the vago-glossopharyngeal, the nucleus of the seventh or facial nerve (originally splanchnic or branchial, now typically somatic), and the motor nucleus of the fifth nerve with its prolongation into the mid-brain.

(4) *Somatic Sensory Nuclei*. The chief representative of this group is the great sensory root of the fifth nerve (Fig. 167). The fibres of this nerve arise from the Gasserian ganglion, pierce the fibres of the pons Varolii, and run to the dorso-lateral part of the pons, where they divide into ascending and descending fibres. These fibres form a cap to the substantia gelatinosa, the descending branches, which are longer, being conspicuous in sections of the medulla as low down as the first or second cervical nerve. This nerve gives common sensation to practically the whole of the head.

It is doubtful in what group we should place the fibres of the eighth nerve. This nerve really consists of two parts very different in function, the cochlear or auditory nerve, and the vestibular or labyrinthine nerve. The fibres of each are derived from ganglion cells in the internal ear, pass to the medulla at its widest part and then, dividing

into two, terminate in masses of grey matter situated at the extreme lateral part of the floor of the fourth ventricle.

The branches of the *cochlear nerve* (Fig. 168) make connection with two collections of cells, the dorsal nucleus, apparently embedded in the fibres of the root itself, and the accessory nucleus, a little triangular mass of grey matter situated in the angle between the cochlear and vestibular nerves. From these nuclei fibres are given off which take two courses. Some, following the previous course of the cochlear nerve, traverse the surface of the fourth ventricle as the *striae medullares* or *striae acusticae*, and then bending inwards pass into the tegmentum of the opposite side. Others pass deeply and form a mass of transverse fibres in the ventral part of the tegmentum, the *corpus trapezoides* or *trapezium*. After making connections with the superior olivary body and a special nucleus, they join the superficial set of fibres, and run up in the tegmentum to the inferior corpora quadrigemina, forming the lateral fillet.

The *vestibular nerve* (Fig. 169) also has two nuclei of termination, the *median nucleus* with small cells, and the *lateral* or *Deiters' nucleus* with large cells. Some fibres pass also to the *nucleus of Bechterew*, which is in close relation with the roof nuclei of the

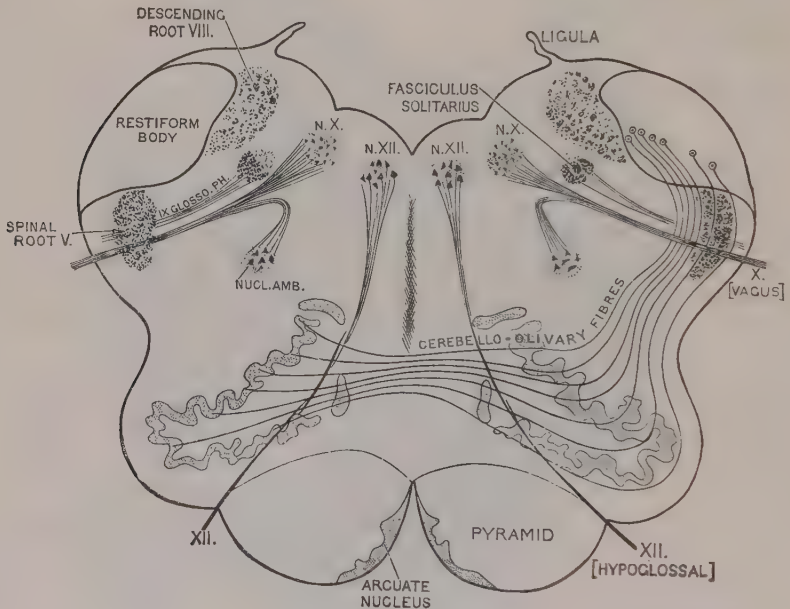


FIG. 166. Cross section of Medulla showing Nuclei of Nerves X and XII. (CUNNINGHAM.)

cerebellum. The descending fibres end chiefly in the median nucleus, while the ascending fibres end in Deiters' nucleus. From the latter a distinct band of fibres travels up to the cerebellum, forming the *median division* of the restiform body, while other fibres run across to the tegmentum of the opposite side, where they take part in the formation of the *posterior longitudinal bundle*.

In a section through the fourth ventricle at about the middle of the pons, a group of large cells is seen in the position occupied by the nucleus of the hypoglossal below. These cells give rise to the fibres of the sixth nerve. Another group is seen lying laterally and more deeply, evidently belonging to the lateral horn system. This is the nucleus of the seventh or facial nerve, the fibres of which pass dorsally and anteriorly, looping round the sixth nerve nucleus, before issuing as the root of the seventh nerve.

In the upper part of the pons we find the fifth nerve (Figs. 163, 164 and 167) with its two roots. The fibres of the sensory root derived from the cells of the Gasserian ganglion bifurcate. The upper divisions, which are short, end in a mass of grey matter at the lateral part of the *formatio reticularis*, the so-called sensory root; while the descending divisions form a long strand of white fibres passing down as far as the second cervical nerve and lying over the *substantia gelatinosa* of Rolando, around the small cells of which the fibres finally terminate. The motor fibres arise partly from the motor nucleus,

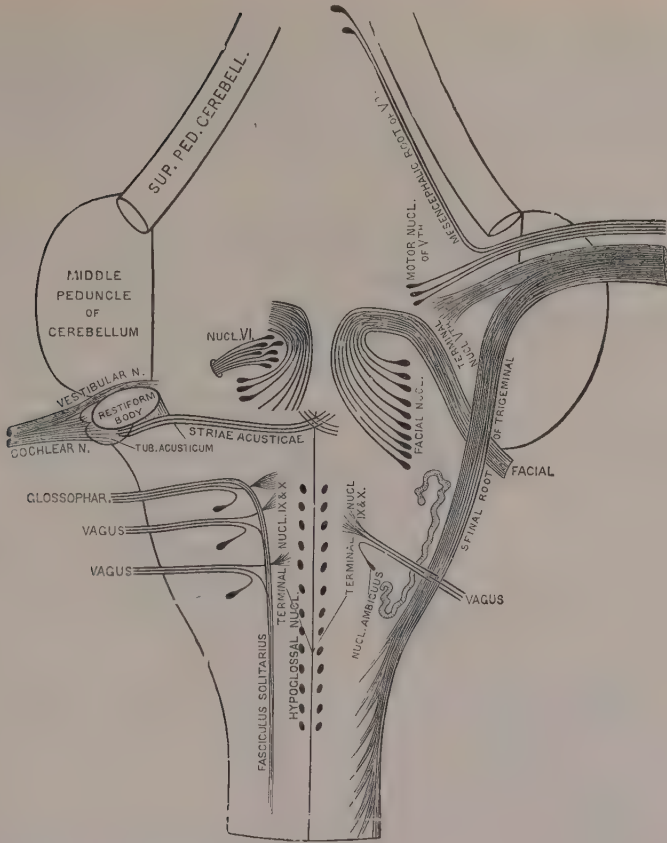


FIG. 167. Diagram showing the Brain Connections of the Vagus, Glossopharyngeal, Auditory, Facial, Abducent, and Trigeminal Nerves. (CUNNINGHAM after OBERSTEINER.)

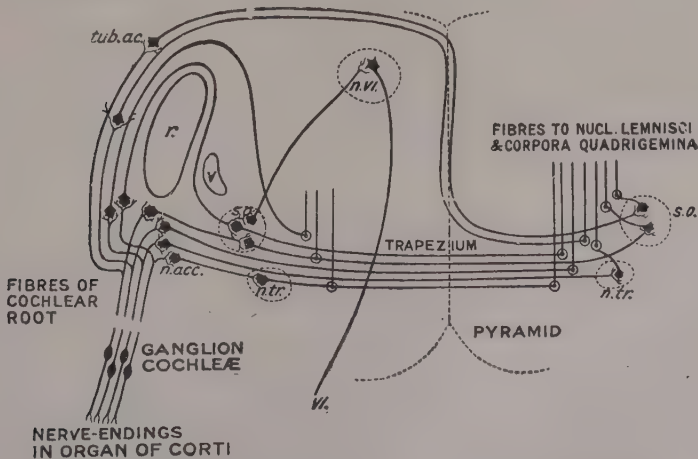


FIG. 168. Plan of the Course and Connections of the Fibres forming the Cochlear Root of the Auditory Nerve. (SCHAFER.)

r, restiform body; *V*, descending root of the fifth nerve; *tub.ac.*, tuberculum acusticum; *n.acc.*, accessory nucleus; *s.o.*, superior olive; *n.tr.*, nucleus of trapezium; *n.VI*, nucleus of sixth nerve; *VI*, issuing root fibre of sixth nerve.

a mass of cells lying internally to the sensory nucleus, and belonging probably to the lateral horn system. A large number are derived from a long column of cells which stretches forward from the nucleus as far as the level of the superior corpora quadrigemina. These fibres are known as the descending motor root of the fifth nerve (Fig. 164).

In the region of the mid-brain, besides the root of the fifth nerve just mentioned, we find only the motor nuclei of the third and fourth nerves, which are situated near the median line in the ventral part of the central grey matter, corresponding in situation to the sixth and twelfth nerves lower down.

SUMMARY OF THE CONNECTIONS AND FUNCTIONS OF THE CRANIAL NERVES

CRANIAL NERVES. The cranial nerves are generally reckoned as twelve in number; 1st, olfactory; 2nd, optic; 3rd, oculo-motor; 4th, or trochlear; 5th, or

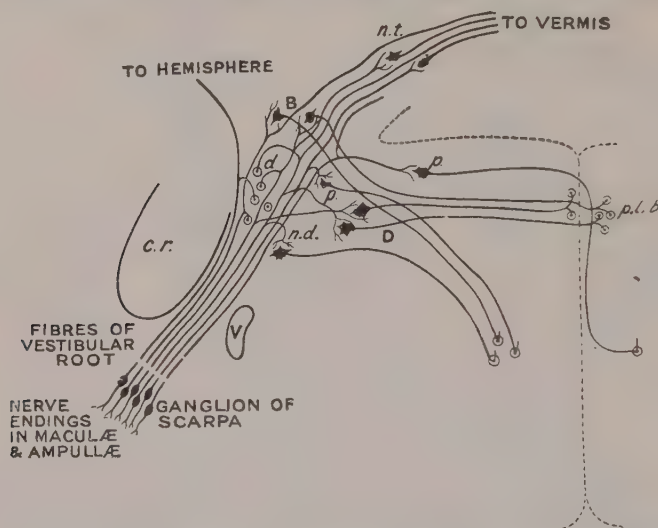


FIG. 169. Plan of the Course and Connections of the Fibres forming the Vestibular Root of the Auditory Nerve. (SCHAFER.)

c.r., restiform body; *v*, descending root of fifth nerve; *p*, cells of principal nucleus of vestibular root; *d*, fibres of descending vestibular root; *n.d.*, a cell of the descending vestibular nucleus; *D*, cells of nucleus of Deiters; *B*, cells of nucleus of Bechterew; *n.t.*, cells of nucleus tecti (fastigii) of the cerebellum; *p.l.b.*, fibres of posterior longitudinal bundle. No attempt has been made in this diagram to represent the actual positions of the several nuclei. Thus a large part of Deiters' nucleus lies dorsal to and in the immediate vicinity of the restiform body.

trigeminus; 6th, or abducent; 7th, or facial; 8th, auditory; 9th, glossopharyngeal; 10th, vagus or pneumogastric; 11th, spinal accessory; 12th, hypoglossal.

Of these the first two stand on a different footing from the rest which, like the spinal nerves, are outgrowths of nerve fibres from the central tube of grey matter surrounding the neural canal or from ganglia corresponding to the spinal posterior root ganglion.

The olfactory bulb and the retinae, from which the majority of the fibres forming the olfactory tract and the optic nerve respectively take their origin, are analogous rather to lobes of the brain than to peripheral sense organs. Thus in the retina there are three relays of neurones through which the visual impulse must pass before it arrives at the optic nerve. The olfactory tract and optic nerve are thus comparable with the association or commissural fibres connecting different parts of the central nervous system. The connections of these sensory fibres, and the structure of the peripheral sense organs will be treated of under the physiology of the special senses. Among the cranial nerves proper we may therefore reckon the third to the twelfth.

The third or oculo-motor nerve arises from an elongated nucleus which extends on either side from the posterior part of the third ventricle along almost the whole length of the ventral part of the aqueduct of Sylvius close to the middle line (Fig. 165). The anterior

part is composed of small cells which give origin to the fibres innervating the intrinsic muscles of the eye, namely the ciliary muscle and the sphincter pupillæ. The rest of the nucleus is made up of large multipolar cells, arranged in groups, and gives origin to the fibres passing to most of the extrinsic muscles of the eye. The fibres of the third nerve pass through the tegmentum to emerge at the inner margin of the crista of the same side. The fibres from the posterior large-celled nucleus supply the following muscles: levator palpebrarum, superior rectus, inferior rectus, internal rectus, and inferior oblique.

Stimulation of the trunk of the third nerve causes the eyeball to look upwards and inwards, with contraction of the pupil and spasm of accommodation.

The nucleus of the *fourth nerve* is situated just behind that for the third, in the floor of the Sylvian aqueduct, on a level with the inferior corpora quadrigemina (Fig. 164). The fibres run from here down towards the pons, then turn sharply backwards to pass into the valve of Vieussens, which they cross horizontally, decussating with the nerve of the opposite side. The superficial origin is therefore from the valve of Vieussens. This nerve supplies the superior oblique muscle of the eyeball. Its stimulation causes the eyeball to look downwards and outwards.

The *sixth nerve*, the motor nerve for the external rectus muscle of the eyeball, arises from a group of large multipolar cells lying on each side of the middle line in the floor of the fourth ventricle. The fibres of the nerve pass directly outwards to emerge from the anterior ventral surface of the medulla between the pyramids and the olivary eminence, at the lower border of the pons. Stimulation of this nerve causes the eyeball to look directly outwards.

All these three oculo-motor nuclei receive collaterals from the fibres forming the posterior longitudinal bundle, many of which are axons of cells in Deiters' nucleus. It is by this means that the contractions of the muscles moving the eyeball are co-ordinated. Sherrington has shown that, although the third, fourth and sixth nerves arise directly from the brain stem and have no ganglion on their course, they are really mixed afferent-efferent nerves. Their afferent fibres, which must arise from the cells in the central nervous system itself, run to the receptor nerve endings with which all the extrinsic eye muscles are richly provided. They are exclusively proprioceptive, and supply no organs outside the muscles innervated by the motor fibres. The occurrence of afferent fibres in these nerves explains the fact previously observed by Sherrington that, after total desensitisation of the conjunctiva by means of cocaine or by section of the first division of the fifth nerve, the ocular movements are carried out with as much precision as in the normal animal. As we have seen, such precision of movement requires the co-operation of afferent impressions from the muscles, and the only possible channels for these impressions are the proprioceptive sense organs and the afferents of the third, fourth and sixth nerve pairs themselves.

The *fifth nerve* or *trigeminal* resembles a spinal nerve in that it has a motor as well as a sensory root. The motor root is much the smaller of the two. The fibres of the sensory root take their origin in the cells of the Gasserian ganglion, which is in all respects similar to the ganglion of a posterior spinal nerve root. The sensory root represents the somatic afferent part of all the motor cranial nerves from the third to the hypoglossal and has a correspondingly wide field of termination in the brain stem. The afferent fibres of the fifth nerve, as they enter the pons, bifurcate like a spinal afferent nerve into ascending and descending branches. The ascending branches are short and pass to an upper sensory nucleus, situated below the lateral part of the fourth ventricle in the upper part of the pons. The descending branches, which are much longer, are collected into one or more bundles which pass downwards in the lateral part of the reticular formation, accompanied by the downward extension of the sensory nucleus known as the *substantia gelatinosa*. The descending root can be traced down in the upper part of the cervical cord, its fibres in this region forming a cap to the gelatinous substance of Rolando. From the cells of the sensory nucleus, fibres pass towards the median raphe, crossing to the other side to take part in the formation of the tract of the mesial fillet (the *trigemino-thalamic tract*). The efferent fibres forming the motor root arise from two nuclei. The chief motor nucleus consists of large pigmented multipolar cells situated just below the surface of the lateral margin of the fourth ventricle at the upper part of the pons. The accessory or mesencephalic nucleus is composed of large unipolar cells, situated in the central grey matter along the lateral aspect of the anterior end of the fourth ventricle, and in a corresponding position in the mid-brain as far as the upper border of the inferior corpora quadrigemina.

The fifth nerve is the motor nerve for the muscles of mastication, and for the tensor tympani and tensor palati muscles. It is the sensory nerve for the whole of the face (including eyeball, mouth and nose). It also contains dilator fibres, derived from the chorda tympani to blood vessels, and is said to have *trophic* functions. The latter

conclusion is from the fact that section of the fifth nerve in the skull is followed by ulceration and sloughing of the cornea, and finally by destructive changes involving the whole eyeball. Since however these results may be prevented by carefully shielding the eye from all dust and deleterious influences, it is probable that the ulceration is merely a secondary consequence of the anæsthesia. The cornea being anæsthetic, foreign objects that fall on its surface are allowed to remain there, and so give rise to injurious changes and ulceration.

The fifth is also said to be the nerve of taste for the anterior third of the tongue, but it is probable that the taste fibres which run in the fifth are derived from the glosso-pharyngeal or from the nervus intermedius.

The *eighth nerve* and its connections have been discussed already. We may here briefly summarise what has already been stated. In describing the eighth nerve it is necessary to consider separately its two divisions, the dorsal or cochlear division and the ventral or vestibular nerve. The fibres of the *cochlear nerve* originate in the bipolar cells of the spiral ganglion of the cochlea. They carry impulses from the auditory end organ. On entering the medulla they bifurcate into ascending and descending branches which terminate in two nuclei, the ascending branches in the ventral nucleus, the descending branches in the dorsal nucleus. The ventral or accessory nucleus lies between the cochlear and vestibular divisions ventrally to the restiform body. The dorsal nucleus, often called the acoustic tubercle, forms a rounded projection on the lateral and dorsal aspects of the restiform body. From these two nuclei new relays of fibres start, and cross the median raphe (where they form the trapezium) to run up in the lateral fillet of the opposite side. From the ventral nucleus the fibres pass directly to the opposite side, forming the greater part of the trapezium, making connection on their way with the nucleus of the trapezium and with the superior olive. From the dorsal nucleus most of the axons pass dorsally, forming the *striæ acusticæ* at the middle of the floor of the fourth ventricle. On arriving at the middle line they dip down and join the fibres of the trapezium of the opposite side. The further course of these fibres up to the internal geniculate body, the inferior corpora quadrigemina, and the auditory radiations of the cerebral cortex, will be described in Chapter XVIII.

The ventral division of the eighth nerve or *vestibular nerve* originates in the bipolar cells of the vestibular ganglion or ganglion of Scarpa. These cells, like those of the spiral ganglion, retain the primitive bipolar character. The fibres divide into ascending and descending branches which become connected with two nuclei. The dorsal or vestibular nucleus, or principal nucleus, which receives the ascending fibres, is a mass of grey matter lying laterally to the vago-glossopharyngeal nucleus and corresponding to the lateral triangular area, the *trigonum acustici*, which is seen on the surface of the fourth ventricle outside the *ala cinerea*. The descending vestibular nucleus, receiving the descending branches of the vestibular nerve, lies below but continuous with the principal nucleus. The fibres of the vestibular nucleus send also collaterals to the nucleus of Deiters and the nucleus of Bechterew, two accumulations of large multipolar cells lying ventrally and internally to the vestibular nucleus, both nuclei being in close relation to the roof nuclei of the cerebellum. Many fibres of the vestibular nerve pass apparently through these various nuclei on the inner side of the restiform body into the cerebellum, where they make connection with the roof nucleus or nucleus fastigii. By the nuclei of Deiters and Bechterew the vestibular nerve is connected through the dorsal longitudinal bundle and the descending vestibulospinal tract with the motor nuclei of the cranial and spinal nerves.

The use of the vestibular nerve is entirely connected with the function of equilibrium. It is not concerned in conveying auditory impressions, all its nerve fibres being derived ultimately from the nerve endings in the saccule, utricle and semicircular canals.

The *seventh cranial nerve* or *facial nerve* emerges from the brain at the inferior margin of the pons, lateral to the point of exit of the sixth nerve. It is almost entirely a motor nerve, but carries also some sensory fibres for taste and general sensibility, which it receives from the *nervus intermedius* of Wrisberg. The motor nucleus of the seventh nerve lies in the reticular formation, dorsally to the superior olive, at some depth below the floor of the fourth ventricle. From this nucleus the fibres first pass inwards and dorsally towards the floor of the ventricle, where they collect to form a bundle which runs upwards in the grey matter for a short distance and then turns sharply in a ventro-lateral direction to emerge on the lateral aspect of the pons. The fibres from the motor nucleus supply the muscles of the face, the scalp and the ear. Secretory fibres also run in the chorda tympani, which is a branch of the facial. These are probably derived, like the sensory fibres, from the nerve of Wrisberg. The sensory fibres of the nerve of Wrisberg originate in the nerve cells of the geniculate ganglion, and passing inwards with the main root of the facial, divide into ascending and descending branches and end

in the upper part of the column of grey matter which receives also the sensory fibres of the ninth and tenth cranial nerves.

The *ninth and tenth cranial nerves* arise by a series of bundles of nerve fibres from the side of the medulla. Both the ninth and tenth are mixed visceral sensory and motor nerves. The sensory nucleus is a column of grey matter lying laterally to the hypoglossal nucleus just below the prominence on the floor of the fourth ventricle called the *ala cinerea*. The descending fibres of these nerves form a well-marked bundle of white fibres known as the *fasciculus solitarius*, or sometimes, from its supposed connection with the regulation of respiration, the 'respiratory bundle of Gierke.' It may be traced down as far as the uppermost part of the cervical cord, its fibres losing themselves on their way down among the cells of the enclosing grey matter. The efferent fibres of the ninth and tenth nerves are derived partly from the dorsal nucleus of the vagus and accessory nerves situated externally to the nucleus of the twelfth nerve, and partly from the nucleus ambiguus, a mass of grey matter lying deeper in the medulla. (Fig. 166.)

The *ninth or glossopharyngeal* nerve supplies motor fibres to the muscles of the pharynx and the base of the tongue, and secretory fibres to the parotid gland. The sensory fibres convey impulses from the tongue, the mouth and pharynx, the fibres originating outside the central nervous system in the ganglion cells of the ganglion petrosum and the ganglion superius. It also contains inhibitory fibres to the respiratory centre.

The *tenth nerve, vagus or pneumogastric*, is joined by the accessory part of the spinal accessory, so that the two nerves may be considered together. It has both afferent and efferent functions:

Efferent functions:

Motor to levator palati and three constrictors of pharynx.

Motor to muscles of larynx.

Inhibitory to heart.

Motor to muscular walls of œsophagus, stomach and small intestine.

Motor to unstriated muscle in walls of bronchi and bronchioles.

Secretory to glands of stomach and to pancreas.

Afferent functions:

Regulates respiration. Stimulation of central end may quicken respiration and promote inspiration, or may inhibit inspiration. Stimulation of central end of superior laryngeal branch causes stoppage of inspiration, expiration, cough.

Depressor and pressor (from heart or aorta to vasomotor centre).

Reflex inhibition of heart.

Its afferent fibres arise from cells in the ganglia on the trunk of the vagus, namely the jugular ganglion and the ganglion trunci vagi. The spinal accessory nerve originates partly in connection with the vagus, partly by a series of roots from the lateral region of the spinal cord as low as the sixth cervical segment. The spinal portion of the nerve is purely motor and supplies fibres to the sterno-mastoid and trapezius muscles.

The *twelfth or hypoglossal* nerve arises from a collection of large multipolar cells in the floor of the fourth ventricle at its lower end close to the middle line. The nerve trunk issues from the ventral part of the medulla in the groove between the anterior pyramid and the olivary body. The hypoglossal is purely motor in function, supplying the muscles of the tongue, the extrinsic muscles of the larynx as well as those moving the hyoid bone.

Since the integrity of the nuclei of the cranial nerves is a necessary condition for the carrying out of various reflex acts in which those nerves are involved, the grey matter of the fourth ventricle and aqueduct is often spoken of as if it were divided into a series of centres distinct for every act. The chief of these are the respiratory and the vasomotor centres. Other centres that may be enumerated are:

Centres for movements of intrinsic and extrinsic ocular muscles.

Cardiac inhibition.

Mastication, deglutition.

Sucking.

Convulsive (connected with respiratory).

Vomiting.

Diabetic (connected with vasomotor.)

Salivary.

Centres of phonation and articulation.

We shall have to consider the action of these centres more fully in treating of the several functions of the body. It must be remembered, however, that when a dozen or more centres are enumerated as being situated in the fourth ventricle, it is not meant that we can anatomically distinguish a group of cells for each act or group of actions

named. When we say that a part of the nervous system is a centre for any action, we merely mean that this part forms a necessary link, or meeting of the ways, in the complicated directing of nerve impulses that takes place in every co-ordinated act.

THE FUNCTIONS OF THE CORPUS STRIATUM

The mass of grey matter known as the corpus striatum, which consists of the nucleus lenticularis and the nucleus caudatus, is the basal part of the outgrowth from which each cerebral hemisphere is formed and in the lowest vertebrata represents almost the whole of the telencephalon. For many years the corpus striatum was classed with the optic thalamus as the 'basal ganglia,' and these two ganglia were regarded as relay stations between the cerebral cortex and the lower parts of the central nervous system. This view was correct so far as concerns the optic thalamus, in which end all the afferent tracts and from which afferent impressions are carried on by fresh relays of fibres to the cortex. In the higher mammals the motor cortex has a direct connection with the motor nuclei of the bulb and spinal cord through the pyramidal tracts, which are not interrupted anywhere on their course. On destroying the corpora striata, degenerated fibres are found running to the optic thalamus, to the red nucleus, and from the latter to the posterior longitudinal bundle. On the other hand the corpus striatum receives fibres from the olfactory tracts and from the optic thalamus. These connections would tend to show that the corpus striatum serves in no way as an intermediary between the cortex and the lower parts of the central nervous system, but is an independent mass of grey matter, receiving impulses from the same source as the cortex and sending impulses which may join in the stream of impressions that play upon the lower motor mechanisms of the bulb and cord.

Isolated excitation of the caudate and lenticular nuclei has no visible effect, provided the current is not so strong as to spread to the adjoining pyramidal fibres in the internal capsule. A study of the evolution of the central nervous system in different classes of animals points to a diminishing importance of these bodies in the normal life of the animal. In the cartilaginous fishes it probably serves to a greater or less degree the same functions in the determination of educated reflexes as the cerebral hemispheres in mammals. In birds the corpus striatum attains its greatest relative development, the increased powers of adaptation in these animals being apparently procured by development of the corpus striatum instead of the pallium or cerebral hemispheres as is the case in mammals. In the monkey, Kinnier Wilson found no definite results to follow destruction of the grey matter in these bodies. The animals were, however, allowed to survive the operation of destruction only three weeks, and the same observer has pointed out that destruction of the corpus striatum in man may give rise to a morbid condition, characterised by tremor in the execution of willed movements and increased tonicities of the muscles. He therefore ascribes to these bodies, or rather to the sensori-motor mechanism which has its chief meeting-place in their nuclei of grey matter, a steadying effect on the motor system, and places this system by the side of the other systems which we have already studied, namely, the vestibular, the cerebellar and the pyramidal systems.

According to Meyer and Barbour, the anterior part of the corpus striatum plays an important part in the regulation of body temperature. In their experiments a metal tube, closed at one end, was introduced through the brain so as to lie in or on the corpus striatum. Through this tube water at any temperature could be passed. It was found that cooling the water gave rise to shivering and increased heat production in the body with a rise of body temperature, while warming the water had the reverse effect. They are therefore inclined to regard this part of the nervous system as representing the chief thermo-tactic mechanism of the body. Magnus, however, finds that temperature regulation is retained in animals in which all the brain in front of the optic thalami has been removed. It is possible that it was really the hypothalamic region which was responsible for the results observed by Meyer and Barbour.

CHAPTER XVIII

THE NERVOUS MECHANISM OF SENSATION

1. GENERAL PHYSIOLOGY OF SENSATION

THE ability to originate sensations is common to almost all parts of the body. Thus the muscles, joints and viscera send nerve impulses to the brain, which record their well-being and activities. We can classify the sense organs into two main groups, those which belong to the common sensibility of the body, and those which form the special senses. The characteristics of the former are (1) that they rarely send impulses, other than those of pain, which pass the threshold of consciousness; (2) that they play a very large part in the initiation of the numerous reflex actions; (3) that when their impulses do reach consciousness they lack definition. The characteristics of the special sense on the other hand are (1) that most of their nerve impulses reach consciousness; (2) that the connection between the stimulus and the resulting response on the part of the individual (as expressed by movements of limbs, &c.) is usually not of the nature of a spinal reflex; (3) that the information supplied to consciousness is very definite both as to quality and intensity.

The indefiniteness of the connection between stimulus and response causes us to depend almost entirely on introspection in our study of the sense organs. But introspection as a method of research has grave disadvantages, for we cannot measure our sensations in terms of physical units. We cannot say how red a rose is or how nice it smells. Neither can we compare the intensity of a beam of light, when we feel its warmth on our skin, with the strength of the stimulus which we receive when it enters our eye. Still less can we judge accurately of the sensations evoked in other individuals or animals when we apply stimuli to them. Because of this difficulty of measuring sensations, two methods of investigation have been developed which to a great extent avoid it, namely the *method of threshold values* and the *method of comparisons*.

In the method of threshold values, gradually increasing stimuli are applied to the sense organ under investigation until a sensation is just perceived. Thus increasing weights are applied to the skin until their pressure is felt, or a light of increasing intensity is presented to the eye until its presence is seen. Such threshold values give definite information concerning the sense organ to which they refer, and allow us to compare the same effects in one and the same sense organ under different conditions and also in different individuals.

In the method of comparisons two separate stimuli are applied, and one or both are varied until the sensations caused by them are equal. Thus a ray of yellow light may be compared with a ray mixed from red and green light, and the intensities of the two adjusted until the sensations caused by both are similar. Both these methods give concordant results if care be taken to make the conditions standard, and both are for this reason largely used for studying the sense organs.

A careful study of these organs is necessary and important because it is only through their agency that we derive information about ourselves, one another, and the world in which we live. The limitations of our sense organs, therefore, restrict our knowledge of the many transformations of energy that are going on around us, except in so far as we are able to devise means of extending them artificially. Thus our knowledge of the existence of ultra-violet light began only with the discovery of photography. Wireless waves circulated through the ether around unknown to us before the invention of the coherer.

CLASSIFICATION OF SENSE ORGANS. Sense organs differ in their anatomical position and structure, and also according to the nature of the stimulus to which they react and the kind of sensation which they cause. Any of these differences might be used as a basis of classification, but the latter is found to be the best.

Structure.	Kind of Sensation.
Skin	{ Touch Pain Heat Cold } Feeling
Eye	{ Light Colour Shape Distance } Sight
Ear	{ Pitch Harmony Position } Hearing
Tongue	{ Acid Sweet Bitter Salt } Taste
Nose	Smell

Stimuli adequate for one sense organ are found to be inadequate for another. Thus sound applied to the ear is adequate, but to the eye is not.

The sense organs appear to be elaborated from a very simple type, and the higher they are developmentally, the more is one kind of stimulus adequate and the less are all others.

Thus the end organs in the cornea react alike by a sensation of pain to touch, electricity, heat, inflammation, &c., while the ear reacts to sound waves only. This specific property of the end organs is also attended by an increase in the strength of response to the chosen stimulus. Thus the retina of the eye can be stimulated mechanically and electrically, but has its greatest sensitiveness to light. It is estimated that the eye is 30,000 times as sensitive to light as any instrument that has been so far constructed. This specialisation of the end organs makes the information which we obtain from them more detailed and complete, but at the same time sets a limitation to the range of stimulus to which each can respond. Thus a pain end organ can react alike to heat rays, visible rays and ultra-violet rays, while the retina of the eye responds to visible rays only.

THE LAW OF SPECIFIC IRRITABILITY. A very little consideration suffices to show that there is no resemblance between a sensation and the stimulus, and that one and the same physical event applied to different sense organs will evoke absolutely distinct sensations. If we take a tuning-fork which is vibrating 100 times per second and apply it to the surface of the skin, we get simply a sensation of vibration, *i.e.* a series of tactile impressions repeated at rapid intervals. If the same tuning-fork be applied to the head, its vibrations are imparted to the bones of the skull and thence

to the auditory nerve endings and arouse in our consciousness a tone sensation of a certain note. The same thing happens if the vibrations of the tuning-fork are conducted by the ear to the auditory nerve endings in the ordinary way through the external and middle ear. On the other hand, it can be shown that different kinds of stimuli applied to one sense organ always evoke the same kind of sensation, if any. Thus a sensation of light may be aroused not only by the incidence of radiant energy of a certain wave length on the retina, but also by electrical or mechanical stimulation of the retina. If the eye be turned inwards and the finger be pressed on the eye through the outer canthus of the lids, a sensation of light is aroused and we see a coloured circle which we refer to some spot lying to the nasal side of the eye stimulated. The character of the sensation therefore bears no resemblance to the physical events by which the sensation is evoked, but depends entirely on the nature of the sense organ which is stimulated. A sensation of light may be produced by any stimulation of the retina, or of the optic nerve, or of the terminations of the optic nerve in the brain. In the same way stimulation of an auditory nerve or its intracranial endings gives rise to sensations of sound.

Where the question has been investigated, it has not been found possible to evoke different qualities of sensation by different modes of stimulation of nerve fibres. It has therefore been concluded that the quality of any sensation depends simply and solely on the termination of these nerves in the central nervous system, and that where sensations of different quality are produced there must also be difference of nerve paths. This idea was formulated by Müller, and is often alluded to as Müller's 'law of specific irritability.' The law states that every sensory nerve reacts to one form of stimulus and gives rise to one form of sensation only; though, if under abnormal conditions it be excited by other forms of stimuli, the sensation evoked will still be the same.

LOCALISATION. Although the different forms of sensation must be regarded as dependent on the integrity of the brain and of its connections with the peripheral sense organs, sensations are not referred to the brain, but are localised as proceeding from some part of the body or from some region outside the body. Thus the sensation of taste is always localised in the mouth; sensation of touch at the skin or surface of the body; while the sensations of hearing and of sight are 'projected,' *i.e.* are interpreted as coming from the environment outside ourselves. Even the organic sensations of posture or fatigue are referred to the peripheral reacting parts of the body and not to the central nervous system. A sensation, therefore, cannot be interpreted as a reproduction of external events, but as a *symbol* of these events evoked by stimulation of the sense organs of the body.

RELATIONSHIP BETWEEN STIMULUS AND SENSATION. Although the sensation is not a reproduction of the stimulus, it is a symbol of the stimulus, and can be used to inform us of events occurring in the world around. Like stimuli, falling on the same end organ, always evoke like sensations, other conditions being equal. An orderly sequence of sensations may therefore be interpreted as indicating a corresponding orderly sequence of physical occurrences in the world around us. Since our sensations are merely symbols of the physical conditions which give rise to them, it is important to inquire how far they correspond *quantitatively* to differences in the energy of the afferent stimuli, *i.e.* how alterations in the strength of stimulus will affect the intensity of the resulting sensation.

THRESHOLDS. Whatever form of stimulus be applied and whatever sense organs be affected, a certain minimum intensity of stimulus is necessary for it to be effective, *i.e.* to produce a minimum sensation. This strength, which

varies with different sense organs, is spoken of as the 'liminal intensity' or 'threshold value' of stimulus or sensation respectively. In each sense organ we can measure the amount of energy which must be applied to it in order to evoke a minimum sensation. This figure varies considerably with the physiological condition of the subject. Thus it is found to vary in most cases with the following factors :

- (1) The rate of application of the stimulus.
- (2) The size of the area to which it is applied.
- (3) Events occurring in the surrounding areas, *i.e.* simultaneous contrast.
- (4) Events which have previously occurred in the area receiving stimulation, *i.e.* successive contrast.
- (5) The time during which the stimulus acts, *i.e.* adaptation.

WEBER'S LAW. It is an interesting question how far the strength of sensation may be regarded as an index to the strength of stimulus. Although it is easy to measure in absolute terms the intensity of a stimulus, and although we can say that such and such a light is stronger than another light, it is impossible to say that the sensation resulting from the stronger is two, three or more times that of the weaker. In measuring the effect on sensa-

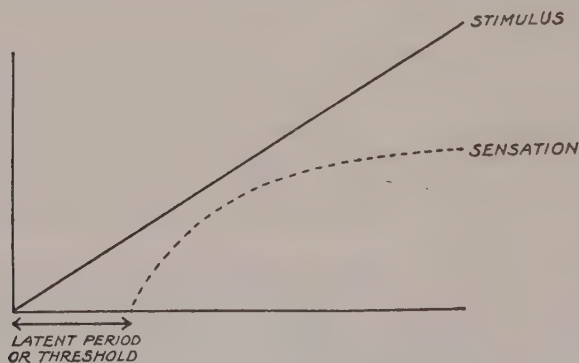


Fig. 170. Diagram to show Relationship between Stimulus and Sensation.

tion of increasing the stimulus, we are therefore reduced to using the *smallest appreciable increase of sensation* as our unit of sensation. Weber's law states that the increase of stimulus, which is necessary to produce an appreciable increase in sensation, always bears the same ratio to the whole stimulus. Thus, if we found that we could just distinguish the difference between a weight of 10 oz. and a weight of 9 oz., it would not be sufficient to add 10 ounces to a weight of 10 lb. in order to produce a distinct difference in sensation. In the latter case we should not be able to appreciate any difference until we had added a pound, *i.e.* one-tenth of the whole stimulus to the weight.

Several methods have been proposed for testing the limits of the applicability of this law. Of these the most important are :

- (1) The method of minimal difference.
- (2) The method of average error.

In the first method we find by trial how much a given stimulus must be increased in order to evoke an appreciable increase of sensation, and this determination is made for a number of stimuli of different intensities. In the second method it is sought to find a strength of stimulus which is just equal to another stimulus of given intensity. It will be found that errors will be made on both sides, and the average error is taken as representing

the minimum difference which is just sufficient to cause a distinct difference of sensation.

In all sense organs Weber's law is applicable only between limits which vary with each sense organ, and it does not hold either for very weak or for very strong stimuli. Within these limits the ratio, which an increase of stimulus must bear to the whole stimulus in order to produce an increase of sensation, may be given approximately as follows for the different sense organs :—

<i>Sense Organ.</i>	<i>Quality determined.</i>	<i>Ratio.</i>
The ear	Difference of intensity	$\frac{1}{9} - \frac{1}{20}$
The eye	Difference of intensity	$\frac{1}{167}$
The skin	Difference of weight	$\frac{1}{20} - \frac{1}{40}$

FECHNER'S LAW gives the result of an attempt to state Weber's law in mathematical terms. It states that the sensation varies as the natural logarithm of the stimulus. This relationship is shown diagrammatically in Fig. 170.

2. VISUAL SENSATIONS

We have seen in a previous chapter that the cerebrum receives fibres from all parts of the body. To the post-central area go the sensations from the limbs, trunk, and head. To the calcarine area go those of vision, to the auditory area those of hearing. We will now consider each of these sensations in detail.

VISION. We shall see (in Chapter XXIII.) that essentially the retina consists of three layers of cells. The outermost is formed of the light-sensitive rods and cones, the middle of bi-polar cells, and the innermost of ganglion cells. It is necessary to keep in mind the fact that the optic nerve and the retina are outgrowths of the brain. The retina should therefore contain all those structures which in every sensory nerve are found to intervene between the sensory cells and the cortex of the brain, namely, first, second, and third order neurons. For example, we shall see later that, starting from sensory cells in the skin, a first order neuron conveys the impulse through the posterior root ganglion into the spinal cord. Here its dendritic endings anastomose with those of the second order relay which conveys the impulses up the cord to the optic thalamus. Here a third order relay starts and takes the impulse to its final destination in the post central sensory area. In the case of sight, the rods and cones are the sensory end organs. The bi-polar cells are the first order relay fibres which convey the impulses to the second order ganglion cells. The axons of these cells pass along in the most superficial part of the retina until they reach the papilla of the optic nerve. Here they turn abruptly backwards, joining similar fibres from other parts of the retina, and pass out, forming the optic nerve. Having entered the cranial cavity the nerve pierces the dura mater and meets its fellow from the other eye; with this it connects, forming the optic chiasma, in which fibres partially decussate. The fibres thus form the optic tracts which travel round the crura cerebri and then divide to end in cells in two different nuclei: (a) The superior corpus quadrigeminum (colliculus), and (b) the external geniculate body. The optic nerve contains four different sets of fibres: (1) Those which convey visual impressions to the brain; (2) those going to the pupillomotor

the right halves of both foveæ which travel *via* the right tracts; (c) those from the left halves of both foveæ which travel *via* the left tracts; and (d) those from the left halves of the periphery of the retina, which also travel *via* the left tracts. The right optic tract thus contains all the visual fibres from the right sides of both retina. These travel to the right calcarine cortex through the external geniculate body of that side. The left tract travels to the left occipital cortex in a similar manner. These connections are represented diagrammatically in Fig. 171.

(2) The pupillomotor impulses travel without crossing to the superior corpora quadrigemina.

(3) Nothing appears to be known as to the fate of the so-called retinomotor fibres; some of them may, in fact, be trophic or vaso-constrictor fibres.

(4) The functions of the inter-retinal fibres are not known definitely. It has been suggested that they cause changes (for example, cone movement) in one retina when light falls on the other. It has also been supposed that the sympathetic inflammation which occurs in one eye after certain injuries to the other, is due to impulses which have travelled *via* these nerves; lastly, binocular contrast and after-images have been ascribed to them.

It is of practical importance to be able to locate an injury to the visual nerve paths. Injury to the optic nerves causes blindness of the eye to which the nerve belongs, and exposure of the eye to light will not then elicit the pupil reflex. Injury to an optic tract causes blindness of the halves of both retina on the same side as the lesion, that is to say, blindness to external objects on the opposite side to the injury. It is interesting to note that, whereas, in most other nerve paths, crossing of the fibres occurs from one side to the other as they travel to the brain, so that the left side of the brain is connected with the right side of the body, this is not the case with the optic impulses. The rays of light have already been crossed and inverted by the optical system of the eye and therefore crossing and inversion of the impulses is rendered unnecessary. Injury to the optic radiation of the calcarine cortex will cause blindness of the corresponding halves of both retina, *i.e.* the half of each retina on the same side, but will not affect the pupil reflex, because the fibres concerned have already turned aside to go to the superior corpora quadrigemina. Injury of the middle of the chiasma, such as may occur in tumours of the pituitary body, affects the nasal halves of both retina and produces double temporal hemianopia.

THE HISTOLOGY OF THE CALCARINE CORTEX. The visuo-sensory area on section presents to the unaided eye a marked white striation known as the line of Gennari, which lies roughly midway between the two boundaries of the grey matter. It is formed by the interlacing dendrites of large stellate cells which replace the external layer of large pyramidal cells found in other parts of the cerebral cortex. This layer of large stellate cells is broad and is the most conspicuous feature of the visuo-sensory cortex. Other noteworthy features are the solitary giant pyramidal cells of Meynert, which are found forming a row of widely separated cells in the internal layer of large pyramidal cells.

PHYSIOLOGY OF THE CALCARINE CORTEX. The anatomical connection of the calcarine area with vision is confirmed by evidence derived from experiment. Movements of the eyes result from stimulation of almost any part of the cortex surrounding the calcarine fissure. If the upper surface of the right calcarine zone be stimulated, both eyes move downwards and towards the left. Excitation of the posterior part causes movement of the eyes up and to the left; while between these two parts there is an intermediate zone, most marked on the mesial surface, stimulation of which

evokes a purely lateral deviation of the eyes to the left. It is, therefore, concluded that there is representation of visual impressions in the cortex around the calcarine fissure.

The conclusions are fully borne out by the results of ablation. Extirpation of the whole calcarine area on one side in animals causes crossed hemianopia, *i.e.* has the same effect as division of the corresponding optic tract.

The probable distribution of impulses from the different parts of the visual field to the cortex is shown in Fig. 172. The right half of the visual field which falls on the left halves of the two retinae is, of course, represented in the left calcarine cortex. In addition it will be seen that the small central part of the visual field has a far larger cortical representation than has the peripheral

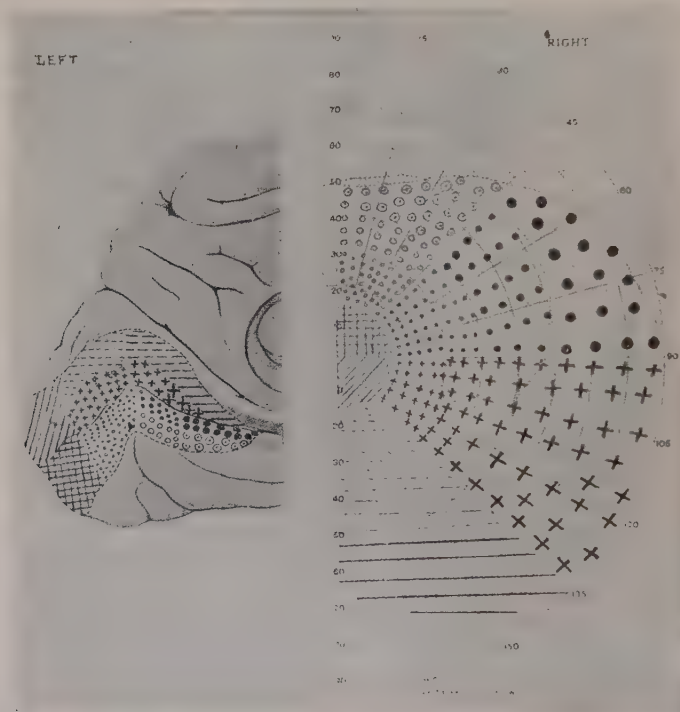


FIG. 172. The relationship between the field of vision and the Calcarine Cortex.
(After GORDON HOLMES.)

part of the visual field. This fits in with the observation that at and near the fovea each visual element, cone (or rod), has its own bi-polar cell and ganglion cell, whereas near the periphery each rod (or cone) shares a bi-polar and ganglion cell with many others. Few nerve fibres, therefore, suffice per unit area of the peripheral retina, whereas many nerve fibres are required per unit area of fovea. The cortical areas vary in a corresponding manner. In this way the fine detail-perceiving qualities of the fovea are provided for in the cortex. Further, it will be seen from the diagram that lower parts of the visual fields, *i.e.* those falling on upper parts of the retinae, send fibres to upper parts of the calcarine cortex, and *vice versa*. This also would be expected since lower parts of the fields of skin sensation are similarly distributed to upper parts of the cutaneous sensory area, and upper parts of the voluntary motor cortex innervate the lower limb.

PRINCIPAL CONNECTIONS OF THE OPTIC TRACTS. For sensations of sight enormous numbers of fibres from second order neurons pass to the external geniculate body and relay there. Third order neurons then convey the impulses to the two calcarine areas. The fibres concerned with the reflex control of the pupil pass from the optic nerves to the optic tracts without decussating, and end by anastomosing with nerve cells in the superior corpora quadrigemina (colliculi). From here short association fibres take them to the pupillomotor centres of both sides.

THE CONTROL OF EYE MOVEMENTS. The efficiency of the eyes as organs of vision depends very largely on the speed and precision with which their axes can be turned in any required direction. These movements are of three kinds: (a) Those in which the eye axes move together to right or left, up or down. (b) Those in which the eye axes move opposite ways, the left eye axis to the right and the right eye axis to the left, thus bringing about 'convergence,' and *vice versa* for 'divergence.' (c) Those in

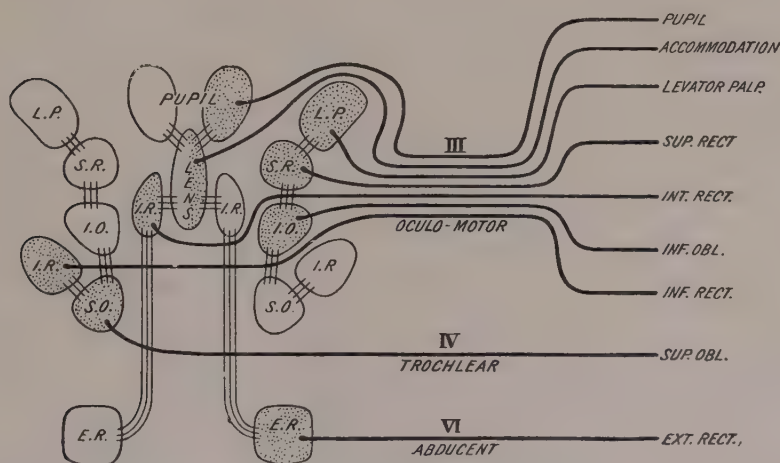


FIG. 173. Diagram to show Relationships of different Points of Oculo-motor Nuclei, and the principal connections between them.

which the eyes rotate clockwise or anti-clockwise about their axes. All eye movements can be analysed into combinations of these three components. The movements may be brought into operation in two ways: voluntarily, *e.g.* the directing of the gaze from line to line of print, as in reading; and involuntarily, as when the eyes turn instinctively to scrutinise an object which has presented itself to the field of view, or when the eyes follow an object as it moves; this movement of the eyes is called the 'fixation reflex.'

Six muscles are available to cause movements of each eye, *viz.*, the four recti and the two obliques. Briefly, each of the recti moves the eye principally in one direction: out, in, up and in, or down and in; while the obliques, at the same time that they direct the gaze up and out (inferior oblique) or down and out (superior oblique), also cause marked rotation of the eyeballs. The eye muscles are innervated by the third, fourth, and sixth cranial nerves, which are derived from nerve cells found in the grey matter of the mid-brain which lies just ventral to the central canal (or Sylvian aqueduct), at the level of the superior corpora quadrigemina. Fig. 173 shows approximately the positions of the various collections of nerve cells which innervate the different muscles.

It will be seen that the third or oculo-motor nerve supplies all the extrinsic eye muscles except three, viz. : Tenon's capsule, which is supplied by the sympathetic ; the superior oblique, which is supplied by the fourth nerve ; and the external rectus, which is supplied by the sixth nerve. Further, while most of its nuclei supply muscles on the same side, two are found to go to muscles on the opposite side, namely, the internal and inferior recti. Another eye muscle also has a crossed connection, namely, the superior oblique (fourth nerve). Of the many bundles of association fibres which connect these different nuclei, the following may be mentioned as being of special importance : (1) From the external rectus of one side through the posterior longitudinal fasciculus to the internal rectus of the other ; thus allowing conjugate deviation of the eyes. (2) Between the nuclei (*a*) of the sphincter pupillæ ; (*b*) of the mechanism for accommodation ; and (*c*) of the internal rectus ; thus co-ordinating the adjustments required for near vision, namely, convergence, accommodation for near objects, and reduced pupil diameter. (3) Between the superior recti muscles of the two eyes ; thus causing symmetrical upward deviation. (4) Between the inferior recti of the two eyes for similar reasons. (5) Between the superior oblique of one eye and the inferior oblique of the other ; thus permitting conjugate rotation of the eyes. (6) Between the superior rectus and the inferior oblique of the same eye ; thus permitting the deviation caused by the one to be corrected by the other. (7) Between the inferior rectus and the superior oblique of the same eye for a similar reason. (8) Between the nucleus of the superior rectus and that of the levator palpebræ of the same eye ; this association permits simultaneous raising of the eyelid with the upward deviation of the eyes, thus preventing any restriction of vision.

Besides these connections between the muscles producing like or associated action there are others equally important between the brain and these centres, namely, those which connect antagonistic muscles. Sherrington showed that, as the muscle on one side of a limb contracts, its antagonist at the same time relaxes, so as to allow the movement to take place smoothly and without waste of energy. This is called 'reciprocal innervation.' The eye muscles show the phenomenon very well. If the right frontal cortex be stimulated, the eyes perform co-ordinate deviation to the left. If now all the muscles of the right eye are divided except the external rectus, it is found that this eye still moves in co-ordination as far as the middle line, through the relaxation of the external rectus muscle.

The orbicularis palpebrarum is also supplied from the third nerve nucleus, for in lesions of this nucleus paralysis of this muscle is found. The fibres innervating it probably travel all the way with the seventh nerve.

CAUSES AND DIAGNOSIS OF STRABISMUS

Squint or strabismus may be caused by a number of conditions : (1) by congenital abnormality ; (2) by interference with the proper rotation of the eyeball ; (3) by injury to one of the external eye muscles ; (4) by injury to or stimulation of one of the nerves supplying these muscles ; (5) by the presence of certain errors of refraction. With regard to nerve injury the following description may be given. Injury to the third nerve causes (*a*) drooping of the upper lid owing to paralysis of the levator palpebræ ; (*b*) external strabismus from paralysis of the upper, inner and lower recti and the unopposed action of the external rectus ; (*c*) rotation of the eye about its visual axis from paralysis of the inferior oblique and therefore unopposed action of the superior ; (*d*) dilatation of the pupil from paralysis of its sphincter and the unopposed action of the dilator fibres which are innervated by the sympathetic ; (*e*) loss of the power of accommodation from paralysis of the ciliary muscle ; (*f*) exophthalmos or protrusion of the eye, caused by the paralysis of so many of its muscles and the unopposed action of the smooth muscle fibres in Tenon's capsule. Owing to the fact that for a considerable

portion of its course the third nerve lies beside the fourth, fifth and sixth nerves, there is usually also some associated symptoms of paralysis in the structures which these nerves supply. Injury to the fourth nerve causes paralysis of the superior oblique, which shows itself by defective movements in a downward and outward direction. Injury to the sixth nerve causes internal strabismus owing to paralysis of the external rectus. This frequently occurs when tumours, hæmorrhage, inflammation or injuries involve the base of the brain. Experimental stimulation of these nerves causes the converse effects to paralysis, which therefore do not require specific description.

When strabismus due to the complete paralysis of one of the recti is present, there is not as a rule any difficulty in ascertaining which muscle is affected. When, however, one of the oblique muscles is paralysed or when the paralysis is only partial, there may be some difficulty in diagnosing the exact condition. It is found, however, that there is a simple method by which the affected muscle may be found. This depends on the principle that, if the eyes are rotated in that direction which requires complete contraction of the affected muscle, the strabismus will be found to get worse, owing to the failure of that muscle being made more pronounced; if on the other hand the eyes are turned in

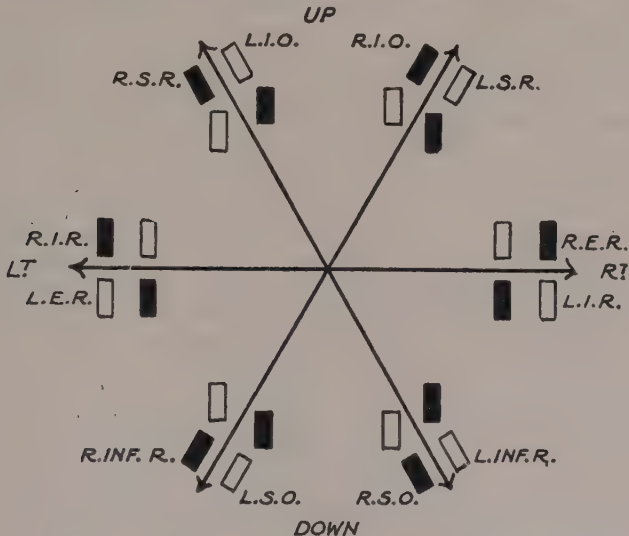


FIG. 174. Showing the Direction in which Paralysis affecting the different Eye Muscles produces Diplopia and the Relative Positions occupied by the True and False Images (HARTTRIDGE).

Black shows image of right eye, white shows image of left eye. The false image is always the one placed furthest from the centre.

the opposite direction, the injured muscle is relaxed and the strabismus vanishes. The following example will show the way the method is used: a man complains of double vision following an injury to the eyes; by directing the gaze in different directions it is found that the double vision increases in amount as the eyes are turned to the right. The injured muscle, therefore, must clearly be a dextro-rotator, that is, the external rectus of the right eye, or the internal rectus of the left. Fig. 174 will be found of assistance, because the arrows which show the directions in which the diplopia increases, point to the names of the muscles, the injury of which will set up the condition which is found to exist. Experience shows that the injured eye is always that to which the more deviated image belongs, and this fact may be readily ascertained by placing in front of the right eye a slip of coloured glass. If the coloured image is found to be the one that is the more deviated, then it is the right eye that is involved in the injury, and therefore in the case that we have been considering, the right external rectus is the injured muscle. Conversely, if the uncoloured image is found to be the more deviated, then the injured muscle is the left internal rectus. In fact it is found in every case that the injured muscle is the one which would give by its contraction that position to the more deviated image which it is actually found to occupy.

TREATMENT OF STRABISMUS. This consists either in the use of suitable prismatic spectacles which will cause a recombination of the double images, or in operative

measures. In the latter, either the tendon of the paralysed muscle is shortened, or that of its antagonist is lengthened, or, better still, a combination of both methods of treatment. Lastly there is a type of strabismus which is found to accompany the refractive errors which cause long and short sight. This type of strabismus, which is called concomitant, is eliminated by correcting the refractive error.

DIPLOPIA is a characteristic feature of a strabismus. Objects appear double to the patient unless or until he has acquired the ability to suppress the images presented to one (usually the weaker) eye. This suppression gives relief from the diplopia, but involves the risk of the loss of function of the unused (suppressed) eye. An eye that has suffered in this way is said to be amblyopic.

Diplopia is also observed when an individual is under the influence of certain drugs, *e.g.* alcohol. It is also seen sometimes when the spherical curvature of the cornea is disturbed by injury or disease, *e.g.* corneal ulcer. In these cases the injured eye sees a double image even when the sound eye is closed, in fact it may see more than two, the condition being called polyopia.

VOLUNTARY EYE MOVEMENTS. The impulses for these originate in the Betz cells of that part of the voluntary motor area which has its centre about two-thirds down, and somewhat in front of the præcentral (Rolandic) strip of cortex. The axons from these cells pass downwards and inwards to form part of the angle (or genu = knee) of the internal capsule. The fibres now descend vertically with the rest of the pyramidal fibres till they reach the level of the superior corpora quadrigemina where, crossing to the opposite side (as all the other pyramidal Betz cell fibres cross lower down) they end in relation to the third, fourth, and sixth nerve nuclei, either directly or by means of short intervening relay fibres. By this crossing of the fibres the cortex becomes connected with the nerve nuclei of the opposite side. Now the right eye is turned towards the left by fibres which originate in the left third nerve nucleus (see Fig. 173). The left eye is turned towards the left by fibres which originate in the left sixth nerve nucleus. Both these nuclei are controlled by impulses which have originated in the right cerebral cortex. In consequence, impulses from the right cortex turn both eyes to the left. But the crossing of the other voluntary motor fibres causes the cortex on the right side to control the left side of the body, *e.g.* the left arm and hand. The turning of the eyes to the left is therefore very appropriate, since it will cause the gaze to be turned towards the side on which other activities may be in progress.

THE FIXATION REFLEX. Fixation is the retention of the gaze of the two eyes on an external object. It is effected by such adjustments of the external eye muscles that an image of the external object remains on the foveæ of the two eyes. These adjustments are carried out with extreme precision and dispatch. The reflex develops at a very early age, since babies a few days old perform fixation perfectly. Two sets of paths are involved in the reflex: (*a*) Those from retina to calcarine cortex *via* the optic radiation; (*b*) those from the calcarine cortex to the superior corpora quadrigemina (colliculi) and from them to the third, fourth and sixth nerve nuclei, probably on the opposite side.

The mode of action of this reflex may be as follows: Suppose an object, *e.g.* an electric lamp, to be voluntarily fixated, the centres of its images will fall on the foveæ of both eyes and the stimulus produced by it will fall partly on the right and partly on the left halves of both retinae. Both right and left calcarine cortices will therefore receive impulses. From these fresh impulses will travel to both right and left sets of third, fourth and sixth nerve nuclei, probably *via* the superior corpora quadrigemina of both sides. The eyes will not be moved since the nerve nuclei on one side would produce a movement which is opposed by that of the nerve nuclei on the other side. Suppose now that the lamp is moved a little to the right. The images

produced by the eye media on the retinae will move to the left and the left-hand halves of the retinae of both eyes will, as a result, be more strongly stimulated than the right-hand halves. In consequence, the impulses reaching the left-hand calcarine cortex will be more powerful than those reaching the right. Stronger impulses will therefore pass down to the superior corpora quadrigemina (colliculi) and so to the third, fourth and sixth nerve nuclei of the opposite side, that is of the right side. In consequence, the eyes will be turned towards the right, and this will cause the centres of the images of the lamp to fall once more on the foveæ. In some such way as this we may picture fixation being preserved.

Ordinarily fixation is under voluntary control. When this control becomes defective, fixation is still effected, but the gaze 'snaps on to' an external object and remains fixed to it. With a great effort the gaze is turned away from this object only to snap on to another. The use of the eyes, *e.g.* in reading, thus becomes impossible, since the gaze cannot be steered along the line of type.

THE CORRELATION OF HEAD AND EYE MOVEMENTS.

These may be of two kinds, compensatory and associated. The compensatory take place when the head is rotated in one direction and the eyes in the opposite direction, in order still to fix the gaze on some stationary object.

The associated movements occur when the head and eyes rotate in the same direction in order to fix the gaze on an object which is moving round the observer. Both these associated movements appear to be controlled *via* the inferior olivary bodies. These bodies are connected (1) to the oculomotor nerve nuclei *via* the central tegmental tract; (2) with the upper cervical segments by the olivo-spinal tract (tract of Helweg); and (3) with the cerebellum. Eye and neck muscles would thus appear to come under the synergic control of the cerebellum.

THE CORRELATION OF LIMB AND EYE MOVEMENTS. For the protection of the eyes there is an important reflex which can be initiated principally by vision but also by the other distant receptors, such as hearing, or even by smell and taste. This involves (a) the firm closing of the lids and in addition, where necessary, the raising of the arm in front of the head (or the hands in front of the eyes); (b) the flexing of the neck and spine so that the face approaches the abdomen; (c) lastly, the reflex may cause the raising of the legs flexed at the knees so that they form an additional protection for the face. This reflex operates through the tectospinal tract which has the following course. Commencing at cells in the superior corpora quadrigemina (colliculi), the axons descend near the posterior aspect of the mid-brain. They then converge on one another and cross in the tegmental decussation of Meynert, at the same time taking a more anterior position near the posterior longitudinal bundle. In this position they descend pons and medulla to reach the cord, and end in the anterior horn cells. A blow aimed at the right side of the head will set up visual impulses in the left halves of the retinae. These will travel to the left superior corpus quadrigeminum, and from here the tectospinal tract will convey them across to the right side and down the right side of the cord, causing raising of the right arm, &c.

3. AUDITORY SENSATIONS

We shall see (in Chapter XXIV.) that essentially the cochlea consists of a mechanism for turning sound vibrations into stimuli applied to the sensory cells. The nerves which ramify among these cells are first order neurons and their cell bodies are found in the spiral ganglion, which is the counterpart of the posterior root ganglion of the spinal nerves. From these cells proceed the

axons which collectively form the acoustic or cochlear portion of the eighth cranial nerve. The vestibular portion of this nerve is not concerned with hearing but with equilibration and will be considered later (see Chapter XXI.). The nerve, having joined the brain at the lower border of the pons, divides into its two parts. The equilibratory part passes into the medulla in front of the inferior cerebellar peduncle while the acoustic part passes in just behind. This part now divides in its turn; the larger portion relays in the lateral principal nucleus (the tuberculum acusticum) which lies behind the inferior cerebellar peduncle, while the smaller portion relays in the anterior accessory nucleus (the trapezoidal body) which lies in front of the inferior cerebellar peduncle (Fig. 175). From these nuclei second order relay fibres cross to the opposite side and form the tract of the lateral fillet (the main ascending sensory pathway). Those from the principal nucleus pass close to the floor of the fourth ventricle (the striæ acusticæ) and then turn outwards, passing across to the opposite lateral fillet. Those from the accessory nucleus

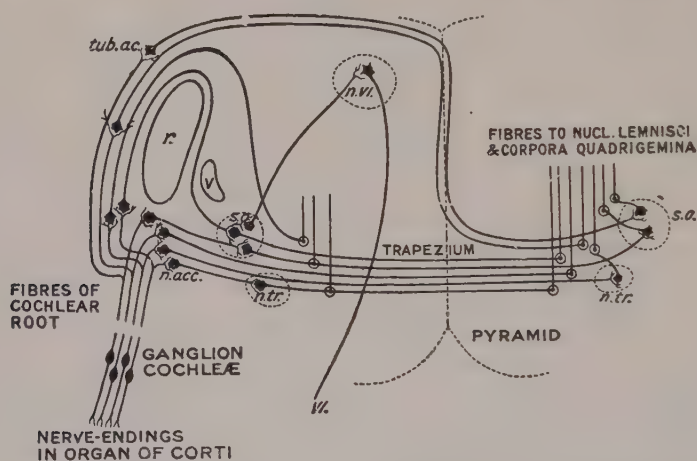


FIG. 175. Plan of the Course and Connections of the Fibres forming the Cochlear Root of the Auditory Nerve. (SCHAFER.)

r., restiform body; *V.*, descending root of the fifth nerve; *tub.ac.*, tuberculum acusticum; *n.acc.*, accessory nucleus; *s.o.*, superior olive; *n.tr.*, nucleus of trapezium; *n.vi.*, nucleus of sixth nerve; *VI.*, issuing root fibre of sixth nerve.

cross those coming from the opposite side, thus forming the trapezium, and also enter the lateral fillet. The second order relay fibres now ascend in the lateral fillet, and the majority end at cells in that part of the optic thalamus called the internal geniculate body (visual fibres are relayed in the external one); here they relay, and third order fibres convey the sensations of hearing to the superior part of the temporal cortex. The minority relay in nerve cells in the lateral fillet and third order relay fibres pass to the inferior corpora quadrigemina. Some also go to the superior olives, and from there pass to the nuclei of the third and seventh cranial nerves either *via* the inferior colliculi, or by a direct connection. These subsidiary but important connections will be considered shortly.

THE AUDITORY CORTEX. The temporal lobe with the exception of its lowest parts has come more and more to be associated with audition. Not only is this function served by the part of the cortex visible on the external surface of the temporal lobe, but also by cortex concealed from view (the gyrus of Heschl) in the depths of the Sylvian fissure. The cortex is

divided physiologically into two parts: (a) The audito-sensory area, and (b) the audito-psychic area.

The audito-sensory area is largely hidden in the Sylvian fissure. A small part, however, is seen at the superior lip of the temporal lobe. Here the stimuli from the cochlea are interpreted as sensations of tone which vary in pitch, loudness and quality. The audito-sensory area is marked histologically by all its layers being very rich in both cells and fibres; particularly is this the case with the outer layer of large pyramidal cells, which are very large and very numerous. So also are the stellate cells in the layer just internal to this. These features are typical of the audito-sensory area. When sections are stained to show nerve fibres they exhibit a band running parallel to the external surface, the line of Kaes.

The audito-psychic area occupies the greater part of the lower two temporal convolutions, *i.e.* it lies parallel with but below the audito-sensory area. Histologically, the cells found are small and there is no line of Kaes. Physiologically, this area must be associated with (a) the interpretation of sounds, *i.e.* the appreciation of music and the correct understanding of the spoken word; (b) the association of sounds with objects, *e.g.* gunfire, fire-alarm, etc.; and (c) the localisation of sound.

THE AUDITORY REFLEX. In animals the incidence of sound on the ears causes erection of the pinnae. This is effected by a reflex, the ingoing path of which consists of auditory nerve fibres, and the outcoming path of fibres of the seventh nerve. In man the external muscles of the pinna have degenerated, and this reflex has been lost. Another lost reflex is the contraction of the sphincter muscle at the base of the pinna which in animals controls the size of the orifice of the external auditory meatus. A reflex, which has been retained, is the contraction of the tensor tympani when sounds first fall on the ear, and this muscle is innervated by a branch of the fifth cranial nerve. This reflex is bilateral even if sounds fall on one ear only. It is most marked for sounds of high pitch. Its object is to put the drum into correct tension for the perception of sounds.

THE AUDITORY PROTECTIVE REFLEX. According to the strength of the stimulus there may be blinking of the eyes only, or, if the stimulus is stronger, blinking and holding the breath. If stronger still, in addition to the above, all movements temporarily cease, whereas for a very loud sound indeed the limbs may become toneless and the body may fall. The mechanism is almost certainly a protective one, to protect the eyes, the respiratory passages, and the body generally. The details of this reflex are not known. The superior olive may be the relay centre for impulses to the tenth cranial nerve for holding the breath, and to the red nucleus or Deiters' nucleus for cessation of movement *via* rubro-spinal or Deitero-spinal tract.

THE AUDITORY EYE-TURNING REFLEX. This reflex is probably caused by impulses which, travelling up *via* the eighth nerve, reach the superior olives or inferior corpora quadrigemina and pass from there to the oculomotor nuclei. The external rectus of one eye and the internal rectus of the other eye are contracted on the side on which the sound has been localised. Some fibres also descend, it is said, to the cervical segments, causing the head to turn towards the sound, as an aid to more accurate auditory localisation or visual observation.

4. SKIN SENSATIONS

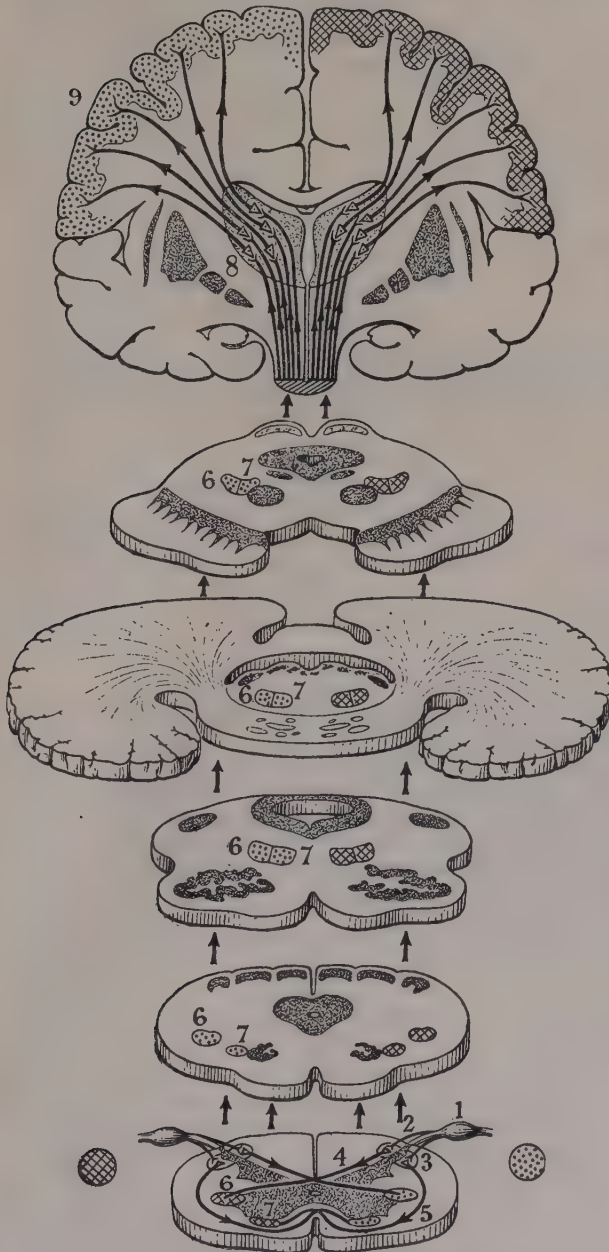
The skin not only forms an extremely important part of the temperature regulating mechanism of the body (Chapter XLII.), but it also forms one of

the principal channels by which sensory impressions are perceived and classified. While eyes, ears, and smell can be referred to as projected senses in that they can perceive qualities which come to the body from a distance away, tongue and skin may be referred to as intimate senses since they perceive qualities in objects which are actually in contact with a part of their sensory structure. The histology and the physiological properties of the sensory end organs will be dealt with later with the other organs of special sense in the chapter on cutaneous sensations. We will now deal in turn with the nerve paths by which the various skin sensations reach their ultimate destinations.

PAIN SENSATIONS. These probably originate in the simple free nerve endings of the dermis and epidermis, these endings being similar in histological character to those so typically found in the cornea of the eye. So far as is known, these endings are the free terminations of the branches of the axon which forms part of the first order relay fibre, the function of which is to conduct the impulses into the cord. These free nerve endings take on many diverse shapes and, although it is possible that they have caps of undifferentiated protoplasm surrounding them, there does not appear to be any evidence for the existence of a special sensory end organ. The axons, originating in these free endings and having formed bundles of nerve fibres, travel towards the posterior root ganglion in which their nerve cells are situated. Having passed through this, they proceed into the cord at its posterior horn. A few fibres proceed towards the anterior horn, to end at cells which will be used for reflex acts, particularly those in response to a painful skin stimulus. For this purpose, similar fibres ascend and descend for a few segments whereby the associated action of other muscle segments is made possible. The main mass of fibres, having ascended the cord for a short distance in Lissauer's tract, end at nerve cells in the soft nerve tissue called the substantia gelatinosa Rolandi. These cells belong to second order relay fibres (Fig. 176). The fibres which originate in them pass across to the other side close to the central canal, and for this reason are particularly liable to be affected by diseases of this structure. For example, in syringomyelia the cystic swellings of the central canal press on and in time destroy the function of these fibres which are conveying painful stimuli across the cord. Having crossed, the fibres enter the posterior bundle of the direct spino-thalamic tract which passes straight up through the cord, medulla, pons, and mid-brain, forming the greater part of the way an important contribution to the lemniscus (fillet). In this manner it reaches the optic thalamus; relaying here, third order relay fibres convey the impulses to the post-central sensory cortex (post-Rolandic area). Here they are distributed in a manner similar to that of the motor areas, *i.e.* legs above, then abdomen, thorax, arm, head, &c. It will have been observed that sensations from the right-hand side of the body have ended at the cortex on the left-hand side of the cerebrum.

TEMPERATURE SENSATIONS. It is believed that heat is connected with the Ruffini endings and cold with the Krause's end organs, curious knot-like terminations of a sensory nerve inside an oval capsule. In accord with this view is the fact that the application of such a drug as menthol greatly reduces and may even abolish the sensations of heat while at the same time it greatly enhances those of cold. The fibres which convey sensations of heat and cold to the sensory cortex travel, so far as is known, by the same route as that taken by the sensations of pain. They reach the cerebral cortex to be distributed in a precisely similar manner as those of pain, so that simultaneous sensations of temperature and pain may be

PAIN, TEMPERATURE AND TOUCH SENSATIONS



Path ascending to cerebral cortex conveying sensations of pain, warmth, cold and touch.

The fibres pass through the posterior nerve roots (1) and enter the cord. Having ascended a short distance in Lissauer's tract (2) the fibres end at cells in the substantia gelatinosa Rolandi at (3). Having relayed, the fibres conveying temperature and pain impulses travel from here near the central canal across to the opposite side (4). They enter the lateral part of the spino-thalamic tract (6) and proceed up this to the optic thalamus (8), where they relay. From here fresh third order fibres convey the impulses of temperature and pain to the post-central cerebral cortex (9). The fibres conveying sensations of touch cross at (5) to the anterior part (7) of the spino-thalamic tract. In this they proceed to the optic thalamus (8), where they also relay. They then proceed to the post-central sensory cerebral cortex (9), conveying touch sensations.

FIG. 176. Direct Spino-thalamo-cortical ascending Pathway for Sensations of Touch, Temperature, and Pain. *N.B.*—The connections are crossed. (BAINBRIDGE and MENZIES' "Essentials of Physiology.")

correlated. Neither temperature nor pain sensations appear to be conveyed at all to the cerebellum.

TOUCH SENSATIONS.—The sensory end organs concerned with sensations of touch are arranged in two different sets, a superficial set and a deep set. The superficial set consists of sensory end organs, probably Meissner corpuscles, found immediately underneath the Malpighian layer of the skin. The deep set consists of a variety of end organs. Of these it is thought that Pacini's end organs are the commonest. Now neurological evidence points to two different kinds of 'touch' impulses being originated in the skin. Some convey highly localised and, from many parts of the body, very exact tactile sensations. Others, on the other hand, convey impulses which may or may not reach consciousness but which quite certainly go in large numbers to the cerebellum and play an important part in kinæsthetic control. Now it is possible that the superficial Meissner corpuscles are concerned with the tactile sensations, whereas the deeper Pacinian corpuscles are concerned with the kinæsthetic control, or both sets may be concerned with both kinds of impulses. Opinions differ on this point, but what is quite clear is the existence of two paths in the cord by which two different sets of impulses travel, namely, those ascending in the posterior columns of Goll and Burdach, and those travelling in the anterior part of the direct spino-thalamic tract. Briefly, the former ascend the cord till they reach the nuclei gracilis and cuneatus in the medulla. From here second order relay fibres cross in the sensory decussation to the opposite side, form part of the fillet (lemniscus), and ascend to the optic thalamus (Fig. 176). Hence third order relays convey the impulses to the post-central cerebral cortex. The latter go straight up to the post-central sensory cortex in the direct spino-thalamic tract, as described above (see Fig. 176).

5. SENSATIONS OF LIMB POSTURE AND MOVEMENT

These sensations have been called by Sherrington "proprioceptive," since they convey information with regard to the condition of the limbs. Some physiologists have called them "kinæsthetic," since they are mainly concerned with sensations which deal with movement and posture. The carrying out of co-ordinated movements involves the employment of two nerve paths: the sensory path from the muscles, joints, bones, &c., to the brain, and, secondly, the motor path from the brain to the muscles. The latter "turns on" the muscle, while the former informs the central nervous system whether the force applied by the muscle has been sufficient in strength and duration to carry out the required act. Not only is the sensory path essential (*a*) for voluntary movements, but also (*b*) for a conscious knowledge of the position of our limbs, (*c*) for a knowledge of the external forces which may be applied to, and (*d*) for the movements which those forces may produce in, our limbs, (*e*) for the correct correlation of the different muscle groups which co-operate to move a limb, whether voluntarily or reflexly, (*f*) for the correct co-operation in time and space of the different limbs in the performance associated, *e.g.*, with walking, and, lastly, (*g*) for a correct estimate of the resistance against which a limb is moving, *e.g.* for the appreciation of a weight held in the hand.

LIMB CO-OPERATION. When kinæsthetic sensibility is defective, there is not only loss in the reciprocal action of the antagonistic muscles which move any one limb, but the ability to perform co-operative movements of different limbs which are needed to carry out a complicated move-

ment is lost. The movements are wrong in amount and are incorrectly timed, resulting in loss of precision. For example, a man can hold the index finger of his right hand one inch above a coin placed on a table. If he now closes his eyes and elevates his elbow until his arm is nearly at right angles to his flank, he can do this still keeping the tip of the index finger in approximately the same position. Such a movement necessitates very carefully judged co-operation between the muscles and joints of shoulder, elbow and hand. Without kinæsthetic sensations such an associated movement would become impossible. Another test of limb co-operation can be described as follows: The experimenter seats himself at a table, holds his hand a short



FIG. 177. A Neuro-Muscular Spindle of the Cat. (RUFFINI.)
c. Capsule. *s.e.* Secondary ending.
pr.e. Primary ending. *pl.e.* Plate ending.
 (All these are probably sensory in function.)

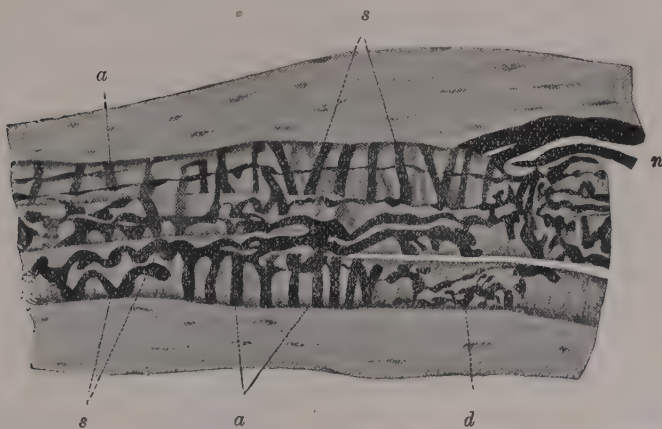


FIG. 178. Part of a Muscle Spindle more highly magnified. (RUFFINI.)
n. Nerve fibres passing to spindle. *s.* Spiral endings.
a. Annular endings of axon. *d.* Dendritic endings.

way above the table with his index finger extended. Now, having closed the eyes, he rises slowly to his feet, extending the arm at the same time so that the finger remains at the same height above the table and is located in the same position as it was at the start. This test also requires co-operation between many muscle groups. Those of the arm and legs may be specially mentioned.

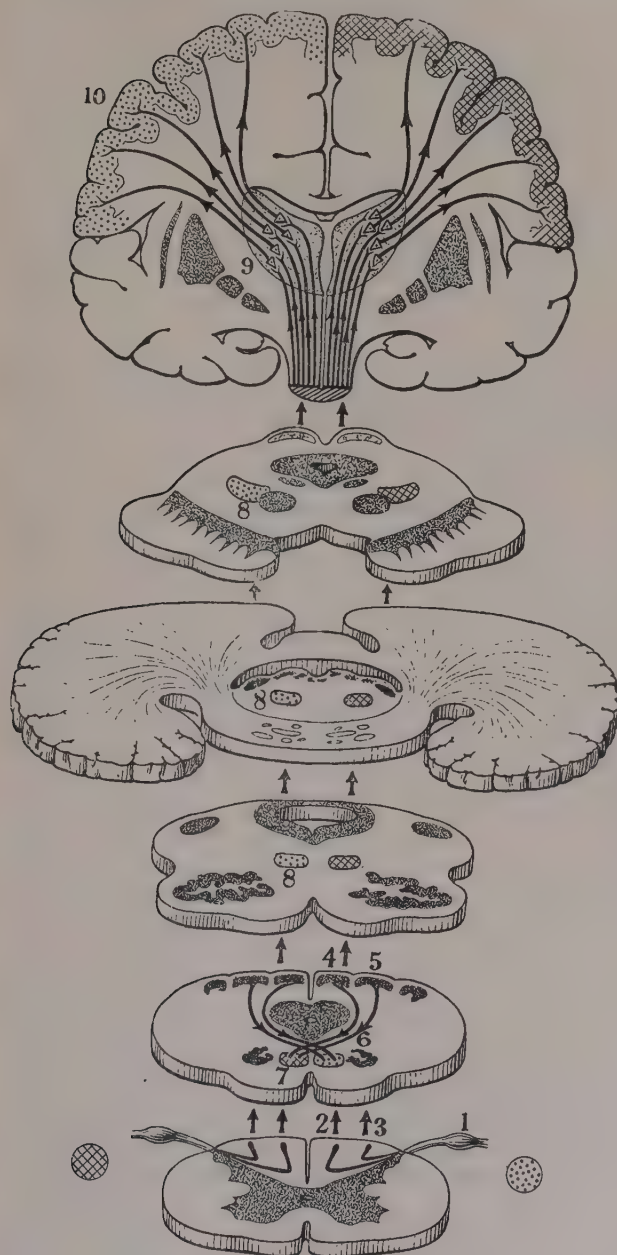
KINÆSTHETIC SENSORY END ORGANS. These are found in bone, tendon, cartilage, muscle, subcutaneous tissue, and other structures which compose a limb. Their histological details are intricate and various. First in importance comes the Pacinian corpuscle, which is found in periosteum, tendons and ligaments, as well as in the mesentery. It is composed of a number of concentric coats, and on transverse section looks not unlike an onion. A nerve fibre ramifies between its layers and it is richly supplied

with blood. Golgi-Mazzoni corpuscles are found in subcutaneous tissue and in tendons, as, for example, in the human tendo Achillis; the nerve terminations end in a brush formation. In the spindles found among skeletal muscle fibres the nerve filaments are coiled round the outside of a muscle fibre, while other sensory nerve terminations in muscle look not unlike the smaller branches of a tree. Some of these are shown in Figs. 177 and 178. It is usually stated that Pacinian corpuscles record pressure, not only the pressure of muscles on periosteum, but also the pressure of one joint-surface on another. They may therefore be used for recording limb position. Muscle spindles, on the other hand, may record either muscle length or muscle tension, or both, while the end organs in tendon presumably record tension only; but not very much is known on these interesting points.

KINÆSTHETIC NERVE PATH.—The impulses originating in the various end organs in muscles, joints and bones, travel to the cord, usually associated in the same nerve with those coming from the cord to innervate the different muscles and those going to the cord carrying sensations from the skin, &c. The number of fibres conveying these limb position and movement sensations varies greatly. Sherrington found that, after section of the motor roots, over one-third of the fibres in a muscular branch remained undegenerated. Some of these may have been sensory fibres to blood vessels and some sensory fibres from, *e.g.*, pain end organs, but the probability is that the greater number were connected with kinæsthetic structures. The nerves are the axons of bi-polar nerve cells situated in the posterior root ganglion; the other axons of the cells enter the cord at the posterior root and end by arborising round cells belonging to second order relay fibres. Cutting these fibres going into the cord results in a loss of sensation of the positions and movements of the limbs, loss of the ability to estimate weights, and movements which have hitherto been finely controlled are now found to be in a state of ataxy. There is loss of postural tone.

Having entered the cord, these kinæsthetic fibres terminate at second order relay cells which occupy at least three different positions (Fig. 179). (A) Cells near the anterior horn which convey impulses to the required muscles either themselves directly or *via* intermediaries. Alternatively, the intermediate relays may end at anterior horn cells of the opposite side. The fibres may ascend or descend a short distance in order to correlate adjoining segments. Paths such as these are tested in the knee jerk or in the tendo Achillis jerk. (B) Cells in the nuclei gracilis and cuneatus in the medulla. To these the kinæsthetic fibres ascend and, having relayed the impulses, cross to the other side to form the mesial fillet. In this they travel to the optic thalamus, where they relay once more and pass to the post-central sensory cortex (Fig. 179). Fibres from the lower part of the body ascend in the tract of Goll to the nucleus gracilis. Those from the upper parts of the body travel in the tract of Burdach to relay in the nucleus cuneatus. Some separation of the fibres is also identifiable in the lemniscus. At the cortex the fibres are distributed in their proper order, which is, of course, legs at the top, head at the bottom, and the intermediate parts of the body distributed between them in order. By impulses travelling up this path the cortex is kept informed of the positions and movements of the limbs. We have seen in the last section that touch, temperature and pain sensations are distributed in a precisely similar manner, and the correlation of these separate sensations is thus made possible. (C) Although, strictly speaking, the fibres going to the cerebellum do not convey sensory impulses and cannot therefore be referred to as dealing with kinæsthetic *sensations*, these impulses do play a most important part, since they enable the cerebellum to carry out

LIMB, POSITION AND MOVEMENT SENSATIONS



Path ascending to cerebral cortex for conveying sensations of limb position and movement.

The fibres pass through posterior root ganglion (1) to enter the cord. They pass up in the posterior tracts of Goll (2) and Burdach (3) to the Nuclei Gracilis (4) and Cuneatus (5) in the medulla. Having relayed here, the fibres pass across to the opposite side by the sensory decussation (6), to turn up at (7) and form a part of the mesial fillet (lemniscus) (8). In this they ascend to the optic thalamus (9). Having relayed here, fibres convey sensations of limb position to the post-central cerebral cortex (10).

FIG. 179. Spino-thalamo-cortical (ascending) Pathway for Sensations of Limb Position and Movement. *N.B.*—The connections are crossed. (BAINBRIDGE and MENZIES' "Physiology.")

efficiently the highly important task of correlating the actions of different groups of muscles and causing orderly limb movements to take place.

THE APPRECIATION OF POSITIONS. A few examples may make clear the importance of the kinæsthetic mechanism that we have outlined. A man seated at a table in such a position that he is unable to see his legs or feet can give an accurate description of the positions of both, no matter whether he has placed them there himself or they have been placed there for him. He can take a typewriter and, if he is skilled, he can write at will without watching the positions of his fingers with relation to the keys. If an experienced pianist, he can play blindfolded or in complete darkness. Skilled acts of this nature require very precise knowledge of limb position and movement. He must know precisely where the limbs are at the beginning, he must then estimate accurately the movements which they make and the positions which they finally reach. Having checked the two latter against one another, he then makes a fresh carefully-estimated movement, once more checks that up against position and proceeds as before.

Voluntary movements, such as these, are greatly dependent for their precision on kinæsthetic sensations. Voluntary control of muscles without this accurate information would be equivalent to an admiral giving orders by wireless to his ships without having any precise knowledge of their whereabouts as a whole or their positions relative to one another. Without this continual stream of accurate information concerning limb position the work of the eyes would be enormously increased. They would have to follow unceasingly the sequences of any skilled operation. A pianist would be unable to read music at sight; he would first have to look at his music, then have to watch the movements of his hands, and then go back to the music again, and so on. It might even be difficult to play with both hands at the same time, and considerable practice would probably be required before playing with more than one finger at a time became possible. The reader must avoid forming the impression that voluntary acts alone require this precise guidance. Such automatic acts as cycling or roller-skating are accompanied by the reception of streams of kinæsthetic impulses by the higher centres. The acts themselves may become entirely subconscious as the result of practice, and yet the movements of the limbs can be accurately followed by the conscious centres. So that a man, for example, who is skating, can give a pupil a correct and highly-detailed account of the positions and movements of the limbs in time and space. Many similar examples could be cited. It is only in such involuntary acts as sneezing, defæcating, or the later stages of swallowing that we have not got precise kinæsthetic sensations. We have not got them probably for the reason that the acts can be efficiently carried out without them. Against this idea of the importance of kinæsthetic sensations for the appreciation of movement and position has been advanced the criticism that we cannot separately estimate the positions and tensions of each individual muscle, but only the limbs taken as a whole. Such an objection is unquestionably based on a misconception. We do not perceive the separate individual molecules which compose a table, but we none the less perceive those molecules arranged to form that object. In the same way, we receive impressions from our limbs grouped in certain patterns, each pattern being associated with a given limb position. These we correlate, when we are babies, by vision, touch, &c. When, in later life, the same kinæsthetic groups of sensations are repeated, we correctly interpret them in terms of given limb positions.

THE APPRECIATION OF RESISTANCE.—If a man walks along a length of flat road and then, having retraced his steps, pushes a loaded hand-cart along the same road, his experiences in the two cases will be quite

different. He feels the thrust of the handle of the cart and correctly interprets it as being equal to the thrust which he himself is applying to the cart by his muscular exertions. He realises that his body as a whole is leaning towards the direction of motion and, in consequence of this, he causes his feet to move to and fro between two positions, which make a considerable angle with his long axis. He raises his feet as he brings them forward much more than he would do if he were not pushing the load. If the handle of the cart suddenly broke, the man in consequence would probably tend to fall on his face. In addition, if the load is heavy he may notice that he is respiring more deeply and, later, he may experience feelings of fatigue. But apart from these factors he has a definite feeling of resistance to his forward progression. How precisely is this feeling aroused? It used to be thought that the individual made a careful estimate of the strength of the motor stimuli sent to the various muscles, of the degree of innervation, as it was called, which was necessary to move the muscles at the required rate. Though there seems to be no contradictory evidence to this idea, there must, however, be additional factors, as is shown by the following experiment. A man is given a number of unknown weights to arrange in the order of their masses. He lifts each in turn, and by repeated trials arranges them in order. He is now told to remain entirely passive during the second half of the experiment. By means of surgical strapping and hooks, arrangements are made for attaching the weights to his wrists. His biceps muscle is now stimulated electrically, thus causing the weights to be lifted. The man finds he can still estimate the relative masses of the weights. Since he is no longer innervating the biceps muscle at all, he must estimate the weights by means of some other factors such as the tensions in the biceps muscle fibres, the biceps tendon, and the pressure between the joint surfaces. The intensity of these varies with the weight lifted, thus enabling an estimate of weight to be made, independent of the "degree of innervation." Resistance to motion, that is, friction, is probably estimated in a similar manner.

APPRECIATION OF PASSIVE MOVEMENTS. Goldscheider measured many years ago the smallest passive angular movement of various joints which an individual could perceive. He obtained the values given in the following table:—

Joint.	Mean Value in Degrees.
Ankle-joint	1.22
Second inter-phalangeal	1.15
First inter-phalangeal	0.89
Hip joint	0.65
Knee joint	0.60
Elbow joint	0.50
Metacarpo-phalangeal	0.39
Wrist joint	0.34
Shoulder joint	0.30

He found, further, that it is necessary that the joint should be moved at a certain rate in order that the movement should be perceived. The values for the different joints are shown in the following table:—

Joint.	Degrees per Second.
Shoulder	0.7
Elbow	1.00
Knee	1.75
Hip.	2.4
Ankle	2.75
Metacarpo-phalangeal	4.0
Wrist	6.0
First phalangeal	12.5

It is clear, then, that the appreciation of limb movements depends on the combination of two factors, the amount of movement performed and the speed at which it is effected. A small movement performed quickly is as adequate for causing sensation as a big movement performed slowly. This compares very closely with the perception of movement of the retinal image. By multiplying together the corresponding figures for each joint given in the above two tables, we obtain what may be called a measure of the performance of each joint so far as passive movements are concerned.

When this is done the following figures are obtained :—

Joint.	Measure of Performance.
Shoulder	0.21
Elbow	0.5
Knee	1.05
Metacarpo-phalangeal	1.56
Hip.	1.56
Wrist	2.04
Ankle	3.36
First inter-phalangeal	11.1

If we compare the performances of the different joints belonging to the upper limb, we see that their performance improves the further they are from the tips of the fingers. This at first sight suggests the idea that the precision of perception of movement given by the shoulder will be spoiled by the low value of the performance given by the more distally-placed joints. Further consideration will show, however, that if the essential thing is the precise appreciation of the position of the fingers, then the further a joint is away from the fingers the longer is the lever attached to it, and correspondingly the greater must be the precision with which it carries out the estimations of position and movement. In the table below are shown the approximate lengths of the levers, measured in inches, which the different joints of the upper limb move. In the second column is shown the performance which those joints should possess in order that the fingers should be moved by each with the same degree of precision. In the last column are given the measured performances of the joints.

Joint.	Length of Lever.	Expected Performance.	Measured Performance.
Shoulder	26	.38	0.21
Elbow	16	0.625	0.5
Wrist	7	1.43	2.04
Metacarpo-phalangeal	3.5	2.86	1.56
Inter-phalangeal	1	10	11.1

A comparison of the last two columns shows that the performance given by measurement corresponds fairly closely with that calculated according to the length of the lever.

It is stated that these estimates of passive movement depend more on joint sensibility than on kinæsthetic muscle sensations. This is based on the evidence that if, when the limb is being moved, tension is applied to it, so as to separate the joint surfaces, the acuteness of perception of movement very greatly decreases. It should be noticed, however, that separating the joint surfaces must also pull upon the muscles and ligaments, and would therefore materially upset any information which the sensory organs in them were

sending up to the higher centres. It seems, therefore, that this conclusion is fallacious and that probably other sensory end organs beside those in the joint contribute information.

THE APPRECIATION OF SHAPE. During the early years of life much time is devoted to the correlation of sight and touch. As a result of this, ideas are established concerning shape, size, position, texture, and visual appearance. This information is made great use of in after-life. Even in complete darkness the correct recognition of objects can frequently be made. Sensations from the tips of the fingers and kinæsthetic sensations from the finger joints co-operate in this recognition. It is of great utility to the blind. The use of the Braille alphabet depends on the ability to educate to a high pitch this power of shape appreciation which depends on the combination of kinæsthetic sensations and touch.

CONTROL OF REFLEXES. The importance of kinæsthetic impulses as a factor in reflex action must now be referred to. If a reflex is set going and the kinæsthetic pathways are intact, a properly co-ordinated and appropriate motor response results. If, however, this pathway be cut or damaged, observation shows that the movement becomes inappropriate, frequently excessive, and sometimes repetitive. Opposing groups of muscles moving the limb are no longer co-ordinated, the give and take of the antagonist muscles is lost, and the reflex becomes somewhat like an engine in which the valve-timing has been disarranged.

LIMB CO-OPERATION. When kinæsthetic sensibility is defective, there is not only loss in the reciprocal action of the antagonistic muscles which move any one limb, but inability to perform the co-operative movements of different limbs which are needed for the effective performance of a complicated reflex or voluntary movement. The movements are wrong in amount and are incorrectly timed, resulting in loss of precision.

The *finger-nose test* is frequently used for testing the efficiency of limb co-operation. To commence with, the patient extends one arm as far behind him as possible. Now, with closed eyes, he attempts to place the index finger as precisely as possible on the tip of his nose. If he achieves this result it indicates that kinæsthetic sensations from structures moving the elbow are properly correlated with those from the elbow, &c. A variation of this test is to ask the patient, with closed eyes, to touch named fingers of one hand with the index finger of the other. Another variation is to ask him to touch the toes of either foot with the index finger of either hand, the eyes being closed during each test.

THE POISE OF THE HEAD. We shall see in Chapter XXI., which deals with the posture of the head, that two important factors, at least, contribute to this function: (1) The sensations from the vestibular organs, and (2) the kinæsthetic sensations from the joints, muscles, and tendons of the neck. It will there be shown that when the position of the body is known, *e.g.* from the information given by the feet when standing on a flat surface, there are three sources of impression by which head position may be judged. (1) Vision; (2) the vestibular organs; (3) the muscles, joints and tendons of the neck. The last really consist of two parts: (*a*) the determination of head poise, and (*b*) the determination of the position of the head relative to the trunk. When, however, the position of the body is not known, *e.g.* when swimming under water, sensations from the eyes and vestibular organs co-operate in the righting of the head, and kinæsthetic sensations can now be used for determining the position of the trunk.

THE PRESERVATION OF THE ERECT ATTITUDE. We shall see in Chapter XXI. that the relative positions of head and trunk may

be gained from the kinæsthetic sensations received from the muscles and joints of the neck. By combining these with appreciation of the position of the head, derived from visual or labyrinthine sensations, the position of the body as a whole may be estimated. Two other factors, however, give important additional evidence by means of which the erect posture may be preserved. These are the sensations from the muscles, joints, tendons, &c., of the legs, and the variations in pressure on the skin and other tissues of the soles of the feet. As a rule, under normal circumstances these sensations co-operate. Experimentally, some of them may be excluded, *e.g.* the eyes, by careful blindfolding, or the sensations from the soles of the feet by standing in a freezing mixture. Experiment shows that equilibration becomes difficult when vision and feet sensations are simultaneously removed. The body sways and may fall unless external assistance is given. With the eyes open this swaying is greatly diminished in amount. This experiment shows that in man, at all events, it is not essential for all these sensations to operate at the same time. Removal of one of them does not seriously derange equilibration. Only when conditions are such that two of them are removed simultaneously are difficulties met with. When walking or running, particularly along a flat surface, the equilibration of the body appears to be easier than when standing still. This is probably because when the body is progressing the feet can be so placed that they span the vertical line drawn through the centre of gravity. Thus, when external forces of unknown duration and force are likely to be encountered, the feet are placed further apart on either side of the body, and the stride decreased so as to give greater stability, *e.g.* when walking or running on a gusty day. Somewhat similar adjustments are made to counteract other difficulties in equilibration, *e.g.* when travelling over an irregular surface, when tired, or when under the influence of alcohol. When external conditions necessitate the placing of the feet in particular positions, *e.g.* when crossing a stream by stepping-stones, considerable skill has to be used. Arm movements may be called into play to aid in equilibration. The pole used by tight-rope walkers is employed for a similar purpose.

CHAPTER XIX

THE NERVOUS MECHANISM OF VOLUNTARY MOVEMENTS

1.—VOLUNTARY MOVEMENTS

LOCALISATION OF MOTOR FUNCTIONS. Histological examination points to a particular area of the cortex as especially connected with motor functions. We have seen that the fibres of the pyramidal tract arise in the Betz cells, which characterise the ascending frontal convolution. If any part of this convolution be stimulated with a weak faradic current, movements are produced on the opposite half of the body, the site of the movements depending on the locality of the spot stimulated. These movements are generally of a character differing from the ordinary postural tonus of the part of the body affected.

It was formerly a subject of dispute whether the movements resulting from stimulation of the cortex were due to the excitation of the grey matter or of the underlying white matter. The following facts show that the seat of the excitation is in the grey matter:—

(1) A smaller strength of current is required to excite the grey matter than the underlying white matter, after removal of the grey matter.

(2) In animals poisoned by chloral the grey matter is inexcitable, though movements can still be aroused on stimulating the white matter. A similar inexcitability of the grey matter can be produced by painting it with cocaine.

(3) The latent period elapsing between the beginning of the stimulation and the occurrence of the movement in the corresponding limb is longer when the grey matter is excited than when the stimulus is applied to the white matter. The results obtained by François Franck give a latent period of 0.065 sec. for the grey matter and 0.045 sec. for the white matter (Fig. 180).

Whether the stimulus acts directly on the pyramidal cells of the cortex, or whether, as seems more likely, it is the endings of the afferent nerves to the

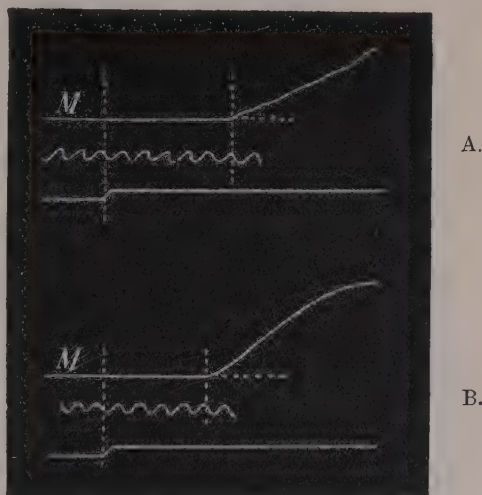


FIG. 180. Tracing to show Latent Periods of Movements obtained by stimulating: A, grey matter; B, underlying white matter of cerebral cortex. Time marking = $\frac{1}{100}$ sec. (F. FRANCK.)

cortex which are really excited by the stimulus, we cannot at present determine.

When we compare different animals, such as the dog, monkey, and man, we find there is a much finer differentiation of movements evoked by stimula-

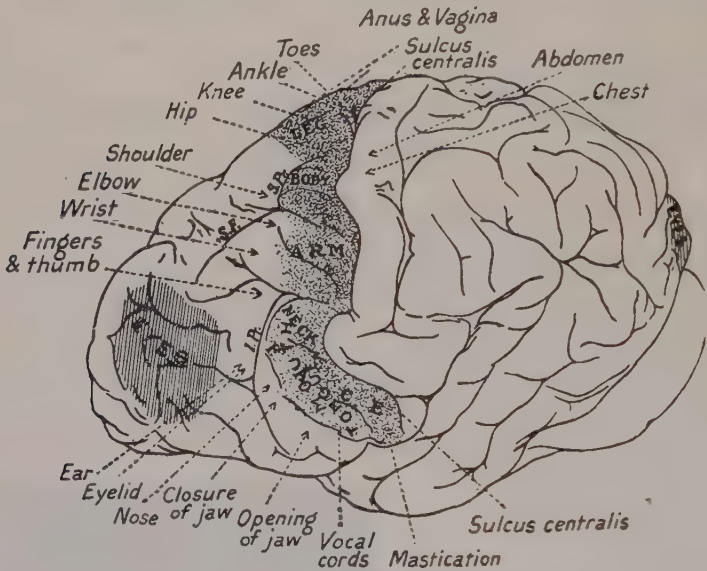
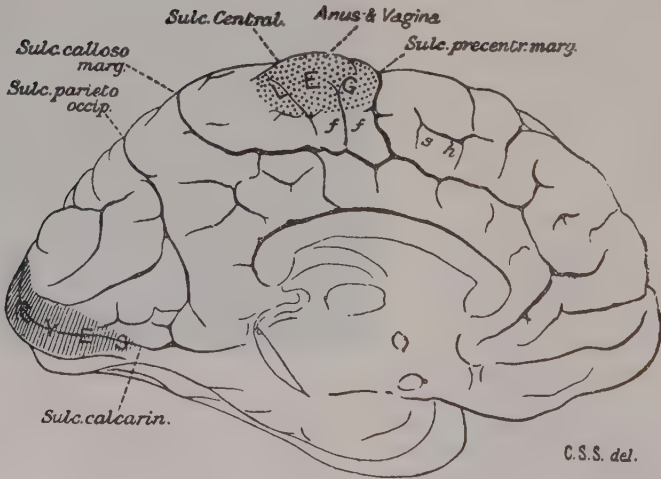


FIG. 181.



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FIG. 182.

FIG. 181. Outer Surface. FIG. 182. Inner Surface of Brain of Chimpanzee, showing Movements obtained by excitation of the motor areas. (SHERRINGTON.)

tion of the cortex in the higher than in the lower type. Whereas in the dog the excitable areas shade into one another, in the higher ape and man the areas are much more circumscribed and are often separated from adjoining areas by an inexcitable zone. The localisation of motor functions in the cortex of the chimpanzee is indicated in the accompanying diagrams by Sherrington (Figs. 181, 182), and Fig. 183 indicates the areas in man. It will

be seen that the motor cortex is limited, on the convex side of the brain, to the precentral convolution, or ascending frontal convolution, situated immediately in front of the fissure of Rolando. On the inner aspect of the hemispheres only the corresponding part of this convolution gives motor responses on excitation. We may say broadly that, from above downwards, by stimulations of the precentral convolution we get movements of the leg, arm, and face; though, as is shown in the diagram, within these larger areas smaller areas can be distinguished for definite co-ordinated movements of the different parts of the body.

NATURE OF MOVEMENTS EXCITED. The movements obtained by excitation of these areas resemble in every respect the co-ordinated movements observed during the normal willed or spontaneous activity of the animal. Like the movements evoked by stimulation of a sensory surface, they involve the reciprocal innervation of antagonistic muscles. Never do we find simultaneous contractions of antagonists, even where two opposing centres are excited simultaneously; one reaction is prepotent, as is the case

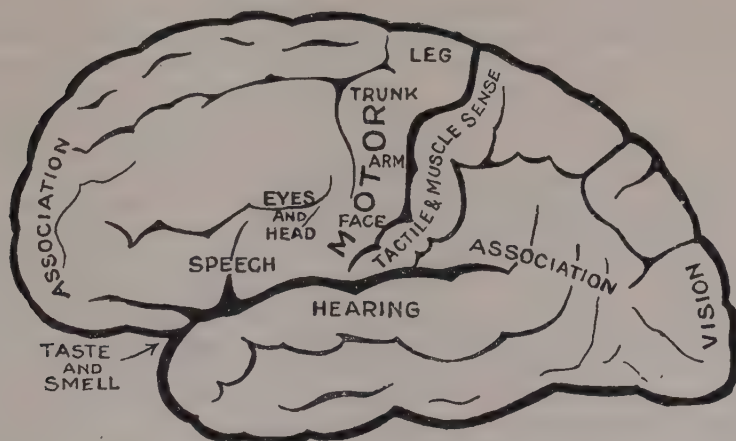


FIG. 183. Diagram showing Localisation of Functions in the Cortex of the Left Cerebral Hemisphere. (BAINBRIDGE and MENZIES' "Physiology.")

of reflexes excited by cutaneous excitation, and this reaction is attended and brought about by ordered contraction of certain muscles, accompanied by an ordered relaxation of their antagonists. Thus the movement of opening the jaw, which can be excited from a fairly large area of the cortex, involves a relaxation of the normal tone of the masseter muscle. Flexion of the leg demands relaxation of the extensor muscles. As in the case of the spinal reflexes, this relaxation or inhibition can be abolished under the action of strychnine or the toxin of tetanus. After administration of either of these it is impossible to evoke inhibition of any muscle. Excitation of the cortical centre for the movements of the jaw causes contraction of both closers and openers of the jaw, *i.e.* a strife in which the stronger masseter muscles predominate, so that the jaw is firmly closed.

The part played by muscular relaxation in the response to cortical stimulation is also well seen in the case of the eye muscles. Stimulation of the centre for eye movements on the convex surface of the frontal lobes on the right side causes 'conjugate deviation' of both eyes to the left. This movement involves contraction of the right internal rectus and left external rectus and

a simultaneous inhibition of the tone of the right external rectus and left internal rectus. If all the muscles of the right eye be divided except the external rectus, this eye looks permanently towards the right side, *i.e.* a right external strabismus or squint is produced. On now exciting the right cortex, *both* eyes move towards the left, although the right internal rectus is divided. The movement of the right eye stops at the middle line, and is brought about simply by a relaxation of the tone of the right external rectus muscle. (Sherrington.)

This movement of both eyes on stimulation of one side of the brain shows that the function of each hemisphere is not entirely unilateral with regard to the muscles of the body. As a rule, the response to excitation of the motor area for limbs is strictly unilateral. In the case of those movements, however, which are normally carried out by co-operation of the muscles of the two sides, such as the movements of the trunk, neck, and eyes, stimulation of the motor area in one hemisphere evokes a movement involving the muscles of both sides of the body, *i.e.* the cortical representation is one of movement rather than one of muscles. Where an action is carried out by similar contractions of corresponding muscles on the two sides, the movement itself is bilaterally represented in the cortex. Types of such reactions are found in closure of the mouth, contractions of the abdominal muscles, extension or flexion of the trunk. It seems that under such circumstances there is a free communication between the lower motor centres of the two sides, since the bilaterality of the response is not altered by extirpation of the cortex of the hemisphere opposite to that which is being stimulated.

The motor phenomena which may be observed as the result of artificial excitation of the motor and sensory areas in the cortex constitute a very small fraction of the activities which must be associated with the cerebral hemispheres. An animal with its cerebral hemispheres intact differs markedly from a decerebrate animal in the variety of combined movements which it may exhibit, either spontaneously or in response to external stimuli. When, however, we excite the motor areas directly, we obtain movements which are practically identical with those which we may elicit from a bulbo-spinal animal by appropriate peripheral stimulation.

The movements excited in decerebrate animals by cutaneous stimulation involve as a necessary factor inhibition of the postural tone as well as co-operative inhibition of the antagonistic muscles. In the same way excitation of the motor area of the cortex has as its most essential feature an inhibitory action on the postural tonus in addition to its excitatory action on the muscles concerned in the movement. A certain antagonism is evident between the total action of the cerebral hemispheres and that of the proprioceptive part of the central nervous system. Whereas in the decerebrate animal there is increased tonus in the masseters, in the neck muscles, the muscles of the trunk and the extensor muscles of the limbs, stimulation of the cortex produces opening of the mouth, flexion of the fore limb or of the hind limb, more easily than any other movements. That an essential part of this action is inhibitory is shown by the effects of exciting the motor area of the cortex after exhibition of strychnine or during the local action of tetanus toxin. In the normal animal closure of the jaw and extension of the fore limb are obtainable only from one or two points on the surface of the brain, but after the injection has been given, every part of the jaw area gives closing of the jaw and every part of the arm area gives extension of the limb.

CORTICAL EPILEPSY. When electrical excitation of any strength over the minimum effective stimulation is applied to the motor area of the cortex, the movements evoked tend to persist for a short time beyond the

duration of the stimulus. On still further increasing the strength of the current, the contraction spreads to adjoining muscles, and finally may affect all parts of the body, giving rise to the phenomenon known as an epileptic convulsion. The same effect may often be caused by weak stimuli if the irritability of the cortex be raised in consequence of previous repeated stimulation. A typical fit consists of two parts. The first effect of the stimulation is a strong tonic contraction; this outlasts the stimulus for some time, and then gives way to a series of clonic contractions, repeated at first at intervals of from six to ten per second, but gradually getting slower as the fit dies away. The tracing of such a contraction is given in Fig. 184.

The main phenomena of a fit, due to irritation of any portion of the motor area, were described by Hughlings Jackson in 1864, even before the experimental proof of cortical localisation had been brought forward by Fritsch and Hitzig. A similar condition may occur in the human subject as a result of irritative lesions of this part of the cortex, such as that due to the presence of a tumour or a spicule of bone pressing on the brain. Jackson showed that in this condition the convulsive movements follow a certain order or 'march.' Thus if the thumb area be the seat of stimulation, the fit begins by a contraction of the thumb muscles, then spreads to the muscles of the hand, fore-arm

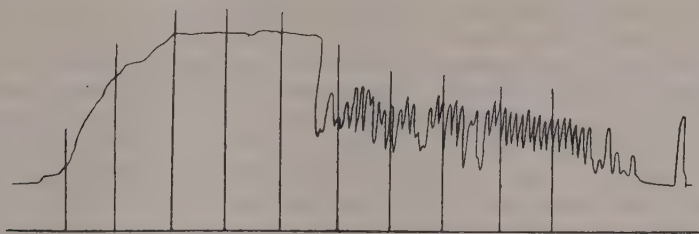


FIG. 184. Tracing of Muscular Contractions during an epileptic Convulsion aroused by Strong Stimulation of the Motor Area. (HORSLEY and SCHAFER.)

and shoulder of the same side, and then to the face, trunk, and leg. If it begins in the toes, the order would be up the leg and down the arm. The same 'march' is observed in artificial stimulation of the motor area. If the convulsions are very strong, they spread to the leg of the opposite side and then to the whole body. The spread to the other side of the body is not prevented by division of the corpus callosum, nor by isolating the centres from one another, so that the sequence seems to be maintained through the mediation of the sub-cortical centres. Complete excision of the cortical centre for any given movement excludes this movement from participation in the fit. In man this type of epilepsy is, in the milder cases at any rate, generally unattended with loss of consciousness. In animals epileptic convulsions can be excited by stimulation of any portion of the cortex, though it is obtained by a weaker stimulus applied to the motor cortex than to any other part. Jacksonian epilepsy is often preceded by a sensation of numbness or tingling, the 'aura,' in the part in which such convulsions begin. In ordinary idiopathic epilepsy tactile or visual sensory auræ may precede the attack; but in this case loss of consciousness is always a prominent symptom, even in the milder form of the disease. Universal epileptic convulsions can be excited in animals by the injection of absinthe into a vein. During the convulsion there is a rise of blood pressure and a quickening of the pulse; the respiration is very often stopped during the tonic part of the spasm, so that the patient becomes livid. The universal condition of excitation affects also the centres from which the secretory nerves originate, so that there is an excessive

flow of saliva, which, in the idiopathic case, is responsible for the characteristic frothing at the mouth.

ABLATION OF THE MOTOR CENTRES

We have seen that a dog may preserve the power of executing reflex movements after ablation of both cerebral hemispheres. We should not expect, therefore, to find lasting paralysis as a result of extirpation of portions of the brain, such as the motor centres. Ablation of the motor areas in these animals gives rise during the first few weeks after the operation to considerable disorders of movement, the muscles on the side of the body opposite to the lesion being markedly weaker than those on the same side. These symptoms, however, gradually pass off, so that after a time not only are both limbs employed in the ordinary automatic movements of progression, but the animal can be taught new movements in the limb, the cortical centre for which has been excised. We must conclude, therefore, that in the dog all the movements, including those which are voluntary and conscious, can be carried out in the absence of the motor centres, although destruction of these centres may impair the accuracy with which some of the finer movements are regulated.

In the monkey (*Macacus*) the effect of ablation is more marked, corresponding to the greater degree of localisation in these animals. If the whole of the motor area on the external surface of the brain be excised, *e.g.* on the right side, there will be almost complete paralysis of the left arm and the left side of the face, and weakness of the muscles of the left leg. The animal will continue to use the leg in walking and in climbing. If the lesion extends to the medial side of the hemisphere, paralysis of the leg is more marked, and the muscles of the left side of the trunk are also affected. Many of these symptoms disappear in the course of time. In a monkey, in which Goltz had destroyed the greater part of the left side of the cerebral hemispheres, it was found that the right arm and hand could still be employed alone for such purposes as taking food, although the movements were much more awkward than those of the left hand.

Still less complete is the recovery from lesions of the motor area in man. We possess now a considerable number of typical histories of cases in which part of the motor cortex has been destroyed by disease or by operation, and the seat of the lesion verified by post-mortem examination. In all these cases there has been a loss of voluntary movement corresponding in distribution to the seat of the lesion, and proportionate in its severity to the extent of the lesion. On the other hand, equally extensive lesions outside the ascending frontal convolution have been shown to have no effect on voluntary movements. The loss is chiefly confined to those movements which we regard as volitional. Although, for instance, the arm may be paralysed, it can still be raised in association with a movement involving the other arm. A certain degree of recovery from the immediate effects of the lesion may be observed, but the recovery is never complete.

The difference in the reaction of various animals to lesions of the motor cortex is connected with the gradual shifting of functions from the sphere of innate reactions to the sphere of educatable adaptations (*i.e.* from the lower centres to the cerebral cortex), which is a characteristic of the evolution of the higher types of nervous system, and is a concomitant of the increased adaptability which distinguishes man from all the lower animals. In the animal without hemispheres, the motor mechanisms for all the movements of the body are present and can be set into action from any point on the

sensory surface of the body. The first effect of adding the cerebral hemispheres to this mechanism is to increase the range of reactions, to modify them or to inhibit them, by diverting the stream of nervous impulses into channels which have to a large extent been laid down in the cortex by the past experience of the individual. In the frog and bird we notice an automaticity and a 'conscious' adaptation of movements to purpose, although the hemispheres have no direct connection with the motor centres of the cord and present no areas which we can designate as motor. In the dog, although a portion of the brain is in direct connection with the spinal motor centres, and can therefore initiate movements without making use of the mid-brain motor machinery, these movements play only a small part in the motor life of the animal, and the removal of the corresponding centres takes away but little of the conscious functions of the animal. In man, the enormous power of acquisition of new movements is rendered possible by the shifting of one motor function after another to the sphere of influence of the cerebral hemispheres. Almost every act of life in man has become one involving co-operation of the cerebral cortex. For many years after birth man is helpless and far inferior, as a reactive organism, to animals much lower in the scale. Even the lower motor functions, such as those of locomotion or defence, have to be painfully learnt, and this learning implies the laying down of paths in the cortex. On this account the subcortical centres in man are no longer complete. Acting in every instance of life as a subordinate or adjunct to the cerebral hemispheres, they are unable to carry out even the simpler motor reactions of the body after removal of those portions of the hemispheres especially engaged in the control of voluntary movement. The motor defect, therefore, which is brought about in man as a result of destruction of one or more of the motor centres, is to a large extent permanent.

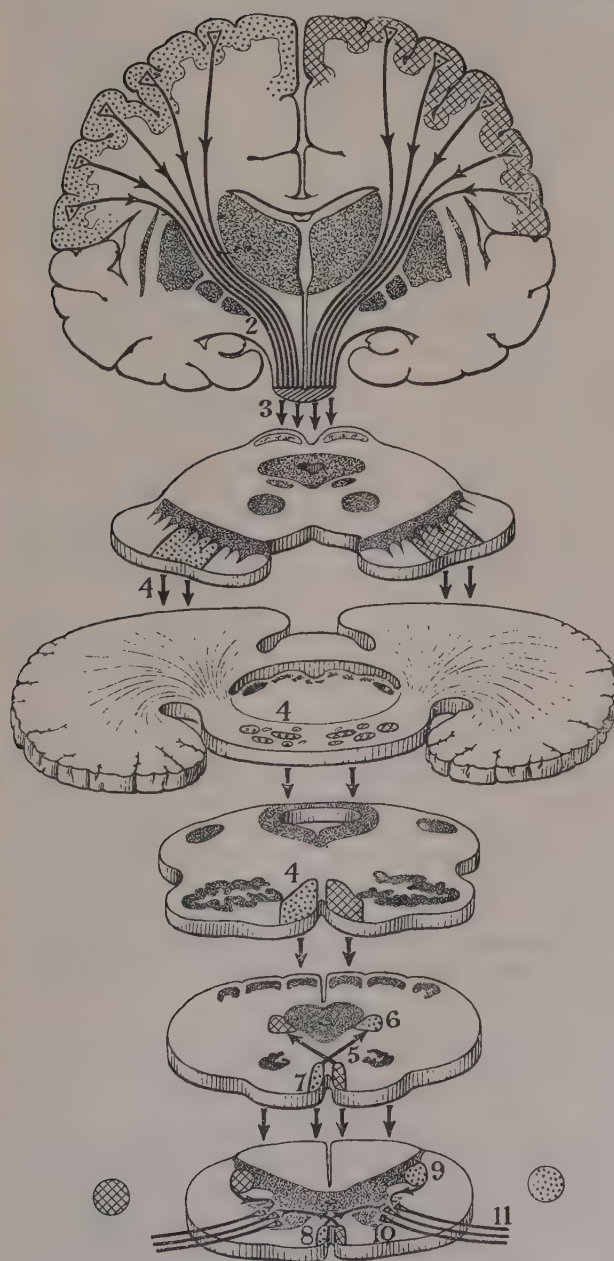
If the lesion in man be strictly limited to the motor areas in the ascending frontal convolution, it is impossible to detect any loss of sensation in the affected parts of the body. On the other hand, some loss of sensation is often found where the paralysis is widespread and occasioned by an extensive lesion in the neighbourhood of the Rolandic area. Moreover, even in localised lesions in man, an epileptic fit may be preceded by a sensory aura in the part which is the starting-point of the convulsive movements. Much discussion has taken place as to the exact significance to be assigned to these slight sensory phenomena. By some observers, *e.g.* Munk, it has been thought that the motor centres were the end-stations of the fibres subserving muscular sensations, and that the movements resulting from their stimulation were due to the revival of such sensations. Bastian insisted on the important part played in voluntary actions by afferent impressions, and these centres have sometimes been spoken of as sensori-motor. The discussion has, however, now resolved itself practically into one of terms. There is no doubt that when the lesion is strictly localised in the motor area, paralysis may be present without any loss of sensation whatsoever. The paralysis therefore cannot be classed with the sensori-motor paralysis distinguished earlier as the result of division of sensory roots. On the other hand, when we say that this part of the brain represents a 'centre for voluntary movements,' we do not mean that the volitional motor impulses arise *de novo* from the pyramidal cells in its grey matter. Every neuron in the nervous system is part of an arc, and it is generally difficult to label any given neuron as definitely sensory or motor. In a reaction involving a chain of neurons, we can assign the name of *motor* to that neuron which sends its axon to the muscle, and of *sensory* or *afferent* to that neuron which receives the impulses at the periphery of the body. Where in the chain we are to

draw the dividing line and to say 'these neurons are sensory and those motor' it is difficult to decide. The motor areas in the cortex give origin to the long fibres of the pyramidal tract, which passes right through the central nervous system to the segmental centres of the cord. We know that the integrity of these tracts is essential for the carrying out of voluntary movement. It is therefore convenient to speak of them as motor or efferent tracts, and of their origin as motor centres, although these tracts have the same relation to the motor cells of the spinal segment as have the afferent fibres from the posterior roots by which similar movements may be evoked.

The activity of the pyramidal cells of the cortex, like that of the motor cells of the spinal cord, is determined by the arrival at them of afferent impressions. Among these the proprioceptive impressions ('muscular sensations') probably play an important but not exclusive part. In the absence of these afferent impressions no spontaneous discharge of motor impulses takes place. Thus in the spinal frog we have seen that complete inactivity is brought about by section of all the posterior roots. In the same way paralysis of the arm is induced by section of all its posterior roots, although it can be shown that the motor cortex is still excitable, and that the application of an induced current to the motor centres of the arm evokes a movement as easily as in the normal animal. The motor cells in the cortical motor centres are normally played upon and aroused by impressions arriving at them from all other parts of the brain and nervous system, and determined originally by impressions falling on the surface of the body.

THE PYRAMIDAL TRACTS. This important bundle of fibres is made up of the medullated axons of the giant Betz cells of the præcentral (Rolandic) cortex. The fibres from the upper part of the cortex destined for the spinal centres innervating the leg muscles run nearly vertically downwards, while those from the lower parts destined for the medullary centres of the cranial nerves innervating the muscles of the eyes and face run almost directly inwards. The bundles of fibres from different parts of the voluntary motor area thus converge on one another to form a compact mass which passes down between the optic thalamus and the corpus striatum, constituting an important part of the internal capsule. The bundles belonging to different regions are grouped together as they pass down through the internal capsule in the order in which they occur in the cortex. At the angle of the genu of the internal capsule (see Fig. 149) are placed the fibres to the nuclei of the eye muscles, then follow in turn, face, arm, trunk, and leg. These bundles collect together in a compact mass, forming the middle portion of the descending main pathway, which passes through the mid-brain lying ventral to the substantia nigra. Retaining the same situation, they reach the pons. They here split up into discrete bundles to permit the cross passage of the pontine fibres. On leaving the pons and entering the medulla they form into two bundles once more. At the lower part of the medulla the main mass of fibres decussates to reach a more dorsal position (the motor decussation), the crossed part being called the crossed pyramidal tract. A remnant of fibres, which is called the direct or uncrossed pyramidal tract, is left behind, close to the anterior fissure. They descend in the cord in these two situations, passing out at different levels to anterior horn cells, the crossed ones to cells of the same side, the uncrossed ones to cells of the opposite side. In this way fibres that have originated in the præcentral motor area on the right-hand side of the brain innervate anterior horn cells which send fibres to muscles on the left-hand side of the body. There is some doubt as to the exact designation to be given to the axons of the Betz cells. Some refer to them as first order relay fibres, and specify that they end in cells near the

VOLUNTARY MOVEMENTS



Path descending from the cerebral cortex for voluntary control of muscles.

From Betz cells of the præcentral motor cerebral cortex (1) the fibres descend in the internal capsule (2), and crura (3), to continue through mid-brain, pons and upper part of the medulla as the cortico-spinal (Pyramidal) tract (4). At the lower end of the medulla the greater part of the fibres pass across in the motor decussation (5) to form the crossed pyramidal tract (6). The smaller part continues towards the cord as the direct pyramidal tract (7). At various levels of the cord fibres from the crossed tract turn off, as at (9), to go to anterior horn cells (10). At various levels of the cord fibres from the direct tract turn off, as at (8), to go to contralateral anterior horn cells, from which the motor fibres proceed to the muscles for voluntary movement *via* the anterior roots.

From the anterior horn cells (10) proceed the motor nerves to the muscles.

FIG. 185. Cortico-spinal (Pyramidal) descending Pathway for Voluntary Control of the Muscles. *N.B.*—The connections are crossed. (BAINBRIDGE AND MENZIES' "Physiology.")

anterior horn, from which second order relay fibres are distributed to the anterior horn itself, from which the third order relay fibres take impulses to the muscles. The difficulty about this view, however, is that it makes the Betz cell axons first order relay fibres, and since these cross in the motor decussation they do what first order relay fibres do not do elsewhere, since crossing is always done by the second order relay fibres. If, however, we refer to the Betz cell axons as second order relay fibres and describe them as terminating at the third order anterior horn cells the question as to the position of the first order relay fibres arises. It is clear that they must be in the voluntary motor cortex itself. There is no difficulty about holding such a view, any more than there is in holding that the bipolar cells in the retina are also first order relays. This latter view has everything to commend it, since the crossing in the motor decussation is now effected by the second order relay fibres, as apparently is done elsewhere in the central nervous system.

IMPORTANCE OF KINÆSTHETIC SENSATIONS. That these play an important part in voluntary movement has already been referred to above. If either the posterior nerve roots or the posterior columns be diseased or injured, marked defects in voluntary movements take place. As a rule, the defect which shows itself is over-action of the voluntary motor centres. The muscles carry the limb too far and they continue working for too long a time. In consequence, this over-action has to be corrected by a succeeding voluntary movement in the opposite direction; this, in its turn, goes too far and has to be corrected, so that instead of the action being effected with precision and dispatch, it consists of a series of attempts to reach the mark, each somewhat better than the preceding one. Careful observation shows that muscle groups do not co-operate properly and that antagonistic muscles tend to contract at the same time; in a word, we have locomotor ataxia. These facts have been mentioned above in the section on limb position sensations.

ANALYSIS OF VOLUNTARY MOVEMENTS. In a voluntary movement, in addition to the contraction in certain muscles and the reciprocal relaxation of their antagonists, other muscles very frequently perform an accessory function. For example, when climbing a rope, using the arms only, the false cords of the larynx are firmly shut (thus 'holding the breath'). In addition, various muscles of the thorax are contracted so as to convert it into a rigid box so that the arm muscles have a firm base on which to work. Another example is the swinging of the arms when walking. The object here is to counteract the turning of the body, which leg propulsion sets up, first to one side and then to the other.

THE TIME RELATIONS OF CENTRAL NEURAL REACTIONS

In the spinal animal a stimulus of any particular quality and localisation always evokes an appropriate reaction. A certain period of time necessarily elapses between the moment at which the stimulus is applied and the moment at which the resulting reaction takes place. This interval is spoken of as the simple reaction time, and in the spinal animal is entirely independent of consciousness. Many reactions, even in the intact animal, are also, as we may say, involuntary and are not modified perceptibly by our consciousness of their occurrence; such reflexes as the withdrawal of the hand when it comes in contact with a hot surface, the shutting of the eyelid when the conjunctiva is touched or the drawing up of the leg when the sole of the foot is tickled. Not only are these carried out in the absence of voluntary impulses,

but in many cases it is almost, if not quite, impossible to check the reaction by any effort of the will.

When the leg is drawn up in response to a painful or nocuous stimulus applied to the foot, a certain amount of time is involved in each of the following links in the chain of processes which determine the reaction :—

(1) The conversion in the peripheral sense organ of the mechanical stimulus into a nerve process.

(2) The passage of a nerve impulse up the nerve from the end organ to the spinal cord.

(3) The passage of the impulse across two or more synapses in the grey matter of the cord.

(4) The passage of the impulse down the motor nerve fibres from the spinal cord to the muscles.

(5) The processes occurring in the end organs of the muscle.

(6) The latent period in the muscle fibre itself.

With a weak stimulus No. 1 is impossible to measure. With a strong stimulus it may be so short as to be practically negligible. (2), (4), (5) and (6) represent quantities for the determination of which we have all the necessary data.

In any given reflex, therefore, we may add these periods together and subtract them from the total reaction time; we thus get a 'reduced reflex time,' which represents the time involved in the passage of the impulse through the central nervous system, and in the conversion of an afferent impulse into an aggregate of co-ordinated motor impulses. It is found that the reduced reflex time accounts for the greater part of the total reaction time. Though we have reason to believe that the rate of passage of an impulse through the finer intra-spinal twigs of a nerve fibre differs appreciably from the rate at which it is conducted by the coarser nerve fibres outside the cord, the chief delay which occurs in the passage of the impulse through the cord must take place either in the nerve cells themselves, or in the synapses through which the impulse passes from one neuron to the next in the chain of reflex elements.

The rate of passage of an impulse through the nerve cell can be determined only in one part of the body, viz. in the posterior spinal root ganglia, since only in these is it possible to detect the moment of passage of an impulse across a given section of a nerve fibre on both sides of the ganglion cell in which the nerve fibres arise. Experiments on this point have been made by Steinach and by Moore. In each case the time occupied in the passage of the impulse through the ganglion was not appreciably longer than if the impulse had passed through a corresponding stretch of uninterrupted nerve fibre. We are therefore justified in concluding that the relatively great delay in the passage of an impulse through the central nervous system has its seat in the synapses across which the impulse has to pass. This conclusion is in accordance with our experience on the latent period of muscle, the greater part of which is due to changes occurring at the nerve endings, *i.e.* in the synapses between motor nerve and muscle.

REACTION TIME. The greater the number of synapses involved in any given reaction, *i.e.* the greater the complexity of the reaction, the longer will be the period which elapses between the moment of application of the stimulus and the moment at which the response takes place. Especially is this the case when the complex meshwork of neurons of the cerebral hemispheres is involved, or when the occurrence of the reaction is associated with the conscious processes of sensation and volition. In the latter case the determination of the *reaction time* has the added interest that it gives

information as to the time relations of the psychical processes which are the representation in consciousness of the physiological changes occurring in the neurons of the central nervous system.

Many methods are employed for the measuring of the reaction time of conscious processes. In most methods the application of the stimulus is arranged so as to close the circuit of a current which flows through an electro-magnet activating a lever which writes on a rapidly moving blackened surface. The reaction of the individual who is the subject of experiment is arranged so that the resulting movement activates a key by which the same current is opened (Fig. 186). We thus obtain a tracing on the blackened surface showing the moment of application of the stimulus and the moment

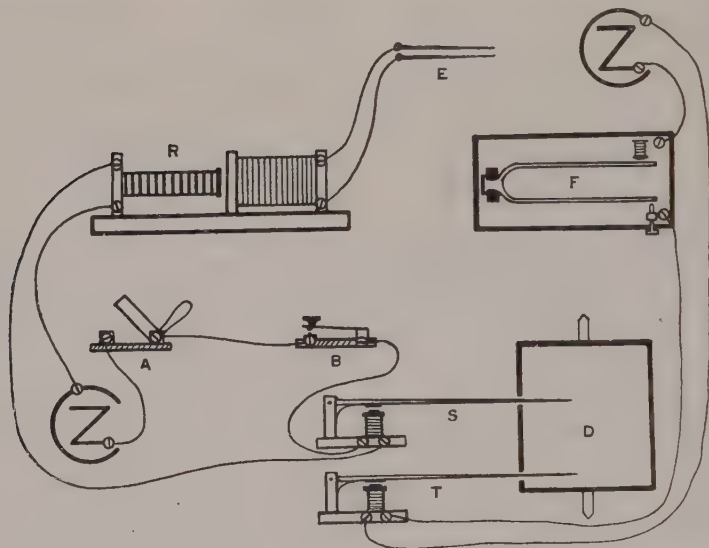


FIG. 186. Arrangement of Apparatus for Determination of Reaction Time for Touch. (ALCOCK and ELLISON.)

R, coil; E, exciting electrodes; F, tuning-fork; A, B, keys; S, T, electro-magnetic signals; D, drum.

at which the reaction takes place. Thus, if the reaction time for an auditory stimulus is to be determined, the electric current is arranged so as to pass through :

- (1) A spring contact key which can be pressed so as to make a noise, *e.g.* to ring a bell.
- (2) An electric signal writing on a rapidly moving surface.
- (3) A second key which the subject will release as soon as he hears the noise of the signal and so break the current.

If the sensory impression is to be from the skin, the current may be made to pass through the primary circuit of an induction coil and wires be taken from the secondary coil to some part of the surface of the skin (Fig. 186). In this case the signal may be started by opening the circuit, and the subject of the experiment will respond by closing the circuit by means of a spring key directly he feels the shock caused by the break of the primary circuit. If the reaction period is to be determined for sight, a piece of white paper may be placed on an electro-magnet in the primary circuit and the person will respond directly he sees this move. Many other instruments have been devised for the same purpose.

The average reaction times in man obtained with the different senses are as follows :—

Sight.	Hearing.	Electrical Stimulation of Skin.
0.186 to 0.222 sec.	0.115 to 0.182 sec.	0.117 to 0.201 sec.

The two figures given for each case are the extremes obtained in different series of observations.

The times vary according to the condition of the person who is the subject of the experiment. They are lengthened by fatigue; they are shortened up to a certain point by continued practice. Within limits also they are shortened by increase of the strength of the stimulus.

DILEMMA. When the subject has to make a deliberate choice between the parts of the body stimulated, the reaction time is considerably longer. To show this, the wires from the secondary coil are connected by a switch to two pairs of electrodes which are applied, one to the right and one to the left half of the body. It is agreed beforehand that the subject shall react only to stimulation, say, of the right side. The switch is removed from the observation of the subject and the stimulus is applied irregularly to one side or to the other. It is found that the additional neural processes involved in determining whether the stimulus is on the right side, and therefore should be followed up as agreed, adds considerably to the length of the reaction time (on an average $\cdot 006$ sec.). It is possible to complicate the dilemma to almost any extent. Thus the experiment may be so arranged that either a red or a white disc appears, and the subject has to react with the right hand to the red disc and with the left hand to the white disc. In such an experiment the reaction time was found to be $0\cdot 154$ sec. longer than the simple reaction time. A still more complex process would be involved in the experiment in which a word was spoken, and the subject had to speak some other word which had some association with the word which formed the stimulus, *e.g.* horse—mammal; paper—pen, &c. In such an experiment the reaction time was found to be as long as $0\cdot 7$ to $0\cdot 8$ sec.

We see that the recording of the time of occurrence of any physical event can occur only after a certain lost time, which represents the observer's reaction time for the stimulus in question. This applies, however, only to movements carried out in response to isolated stimuli or to stimuli repeated at irregular intervals. When the stimuli are rhythmic the lost time applies only to the first one or two of the stimuli. The observer or subject is conscious of the interval elapsing between the physical event and his reaction, and anticipates the later stimuli so that his reaction becomes synchronous with the stimulus. This synchronism of stimulus and reaction characterises all rhythmic movements, such as dancing or the playing of an orchestra in time with the beat of the conductor's bâton.

2.—GROUP CONTROL

THE CEREBELLUM.—The cerebellum forms an important organ occupying the posterior part of the cranium. Its weight is approximately one-tenth that of the whole brain. It consists of two lateral lobes, having an intermediate lobe, the vermis, between them. The two halves are joined by the pons which surrounds the brain stem at the level of the fourth ventricle. It commences in early foetal life as a small elevation in the dorsal wall of the neural canal, and rapidly grows, being thrown into a number of folds and having several important masses of grey matter inside its substance. Small and simple in structure in fishes and amphibia, it shows an increasing complexity and size as one passes up the mammalia to reach its highest development in the higher apes and man. Like the cerebrum, its external surface is composed of grey matter with numerous medullated white fibre masses underneath. The folds run in such a way as to seem to divide the organ into a number of laminae. The interior

masses of grey matter consist of the *nucleus dentatus*, the *nucleus emboli-formis* and *nucleus tecti*. These consist of important collections of cells resembling in many ways the nuclei of the motor nerves. The cerebellum connects with the rest of the central nervous system by means of three pairs of peduncles: the superior peduncles or brachia conjunctiva, the middle

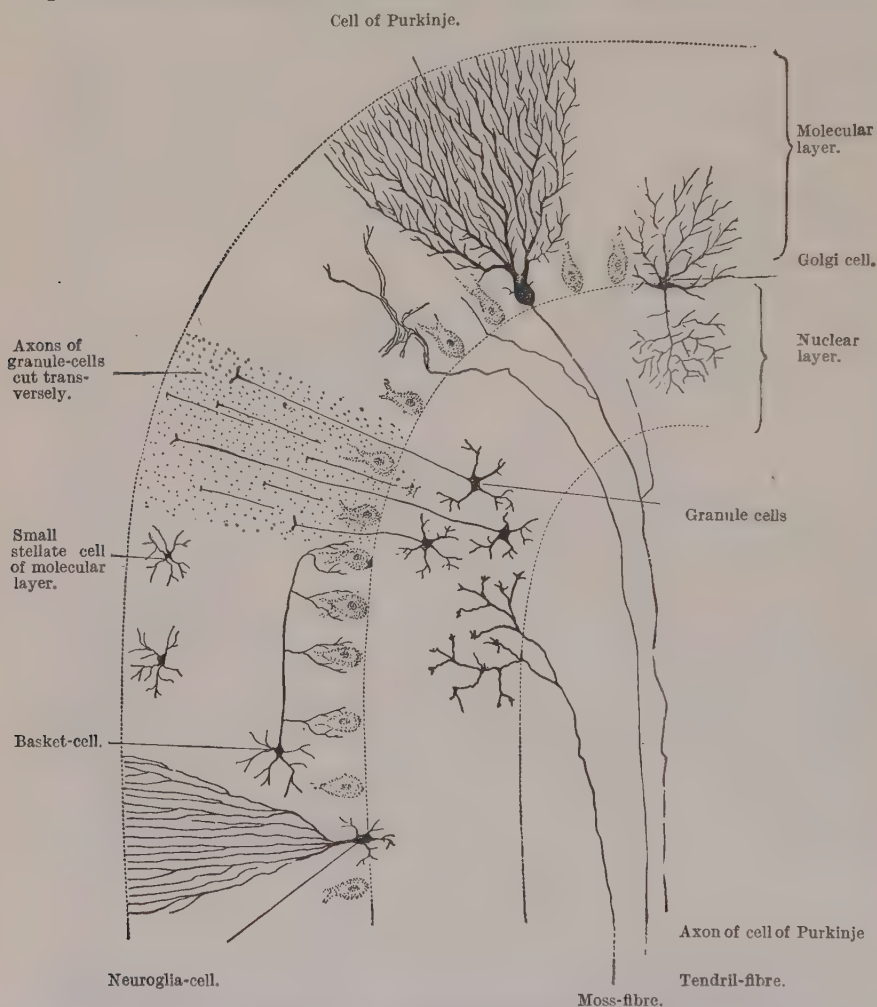
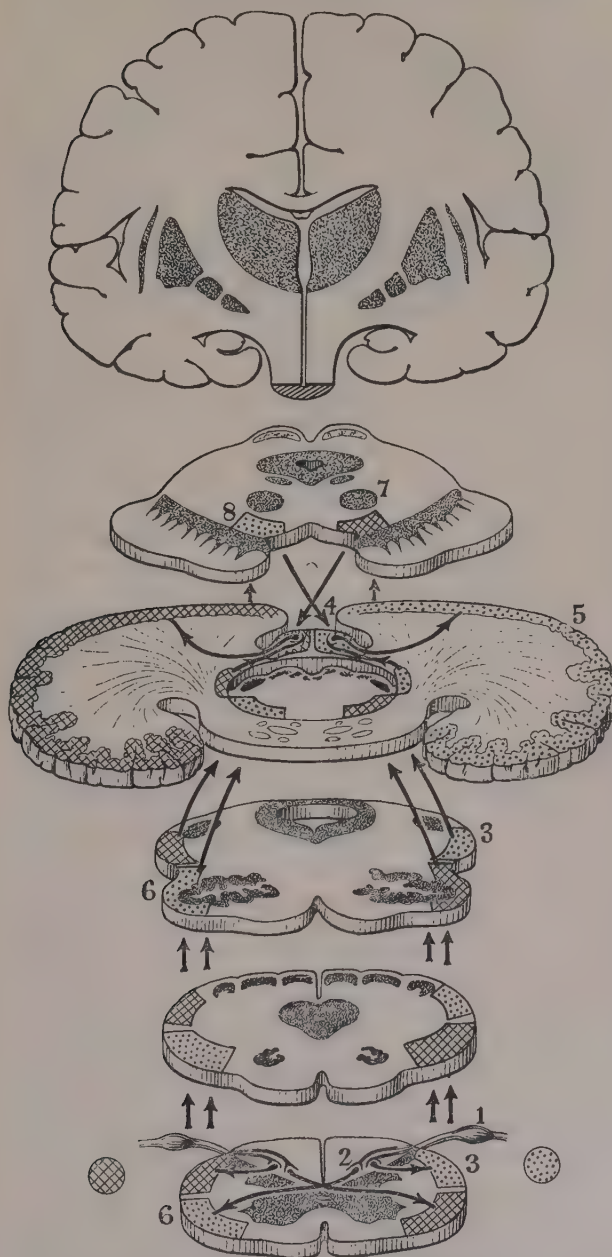


FIG. 187. Transverse Section of a Cerebellar Folium. (GRAY'S "Anatomy.")

peduncles, which joining together form the pons, and the inferior peduncles or restiform bodies.

THE HISTOLOGY OF THE CEREBELLAR CORTEX. The grey matter consists of two layers: an outer molecular layer which presents a slightly granular appearance with few nuclei. Internal to this is the granular layer, which is composed of numerous small nerve cells. Internal to the second layer is the central core of white matter of the cerebellum. At the line of junction of the molecular and granular layers there is a single row of closely-placed large flask-shaped *cells of Purkinje*. Each of these has one apical dendrite which is distinguished from all others in the central nervous system by the richness of its branchings. These ramify in a tree-like manner

GROUP MOVEMENT CORRELATION



Path ascending to cerebellum from limbs for the correlation of group movements.

The fibres pass through the posterior roots (1) and enter the cord to end at cells in Clarke's columns (2). Starting from these cells most fibres enter the direct cerebellar tract (3); in this they ascend *via* the inferior cerebellar peduncle to end at the vermis of the cerebellum. (4). The fibres from here pass to the cerebellar cortex (5). Fewer fibres starting from Clarke's column of cells (2) cross to the other side and enter the crossed cerebellar (Gowers') tract (6). In this they ascend until they reach the level of the red nucleus (7). Here they turn down into the superior cerebellar peduncle (8), cross in the brachia conjunctiva at (4) to end at the vermis. The next relay of fibres goes to the cerebellar cortex (5). The double crossing causes the impulses to end in the cerebellum on the same side as that on which they started, as do those that have travelled up the direct cerebellar tract.

FIG. 188. Spino-cerebellar (ascending) Pathway for conveying information to the Cerebellum of the positions and movements of the Limbs. *N.B.*—The connections are homolateral, *i.e.*, either uncrossed or twice crossed. (BAINBRIDGE AND MENZIES' "Physiology.")

towards the external surface of the molecular layer as shown in Fig. 187. In addition, the molecular layer contains small star-shaped cells, *basket cells* and neuroglial cells. In addition to the Purkinje cells, *Golgi cells* also lie on the junction between the molecular and nuclear layers. The nuclear layer will be seen to contain granule cells which send their axons into the molecular layer.

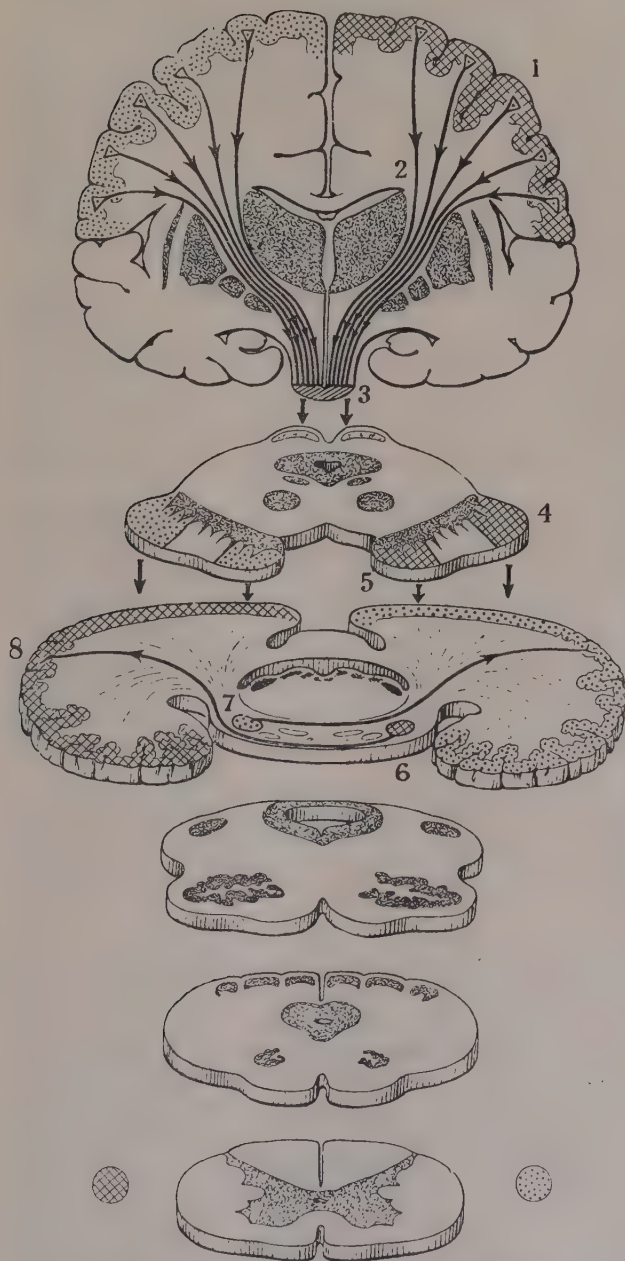
Impulses enter the cerebellar cortex by two different kinds of termination; *moss fibres*, so called from the curious thickenings which they present, pass into the grey matter and terminate by frequent branchings in the nuclear layer, and *tendril fibres*, which end by arborising richly round the bases of the dendrites of the cells of Purkinje. Impulses leave the cerebellar cortex by the axons of the Purkinje cells. These acquire a medullary sheath, enter the white matter, and end by arborising round cells in the important central ganglion of the cerebellum, the *nucleus dentatus*. The above description gives us an idea of the extreme complexity of the possible paths open to nerve impulses traversing the cerebellar cortex. Thus a cell of Purkinje may be excited by an impulse which has entered by a tendril fibre; or by one which, having ascended by a moss fibre, is conveyed by one or more granule cells to the dendrites of the cells of Purkinje; or *via* moss fibres and granule cells as above to basket cells in the molecular layer which convey the impulses to one or more Purkinje cells. The moss and tendril fibres appear to convey impulses which might originate in most of the receptor apparatus of the body, including vision and hearing, but possibly excluding taste and smell. On the other hand, the axons of the Purkinje cells convey impulses which go to the red nucleus and thence down the spinal cord for the supply of the anterior horn cells. Further details of these connections will now be given.

FIBRES TRAVELLING TO THE CEREBELLUM. (1) Kinæsthetic impulses from muscles, joints, tendons, &c., enter the spinal cord *via* the posterior root ganglion. The fibres terminate at Clarke's column of cells. Second order relay fibres starting here convey the impulses up the postero-lateral (or direct) cerebellar tract of the same side. This ascends straight into the inferior cerebellar peduncle to terminate in the vermis on the same side. From this, third order fibres appear to end in the cerebellar cortex in moss or tendril fibres (Figs. 187 and 188). Some of the axons originating in Clarke's column of cells cross to the opposite side of the cord, and travelling in the antero-lateral cerebellar tract (Gowers' tract) ascend to the level of the red nucleus, where they turn abruptly downwards, enter the superior cerebellar peduncles, cross with these to the same side as that on which they started, and go to the vermis. Here they relay and, as third order fibres, are distributed in the cerebellar cortex (Fig. 188). These kinæsthetic sensations form a very important part of those going to the cerebellum.

(2) Skin sensations, which have entered with the posterior roots, travel up in the columns of Goll and Burdach to relay in the nuclei gracilis and cuneatus; from here, second order fibres pass probably as superficial or deep arcuate fibres to the inferior cerebellar peduncle of the same side. They relay in the vermis, and, as third order fibres, end at the cerebellar cortex (Fig. 190).

(3) The cerebrum sends two important sets of fibres to the cerebellum, the frontal and the temporo-occipital cerebellar tracts. These descend on either side of the pyramidal tracts until they reach the pons. Here they relay with cells lying in the pons itself, from which second order relay fibres end in the vermis on the opposite side. From this, third order relay fibres pass to the cerebellar cortex. It is by means of these fibres that voluntary impulses are subjected to the synergic control for which the cerebellum is largely responsible.

GROUP MOVEMENT



Path descending from cerebral cortex to cerebellum for initiating movements of muscle groups.

For voluntary group movements the fibres start at the frontal cortex. For group movements initiated by sight and hearing, fibres start at the calcarine and temporal cortex (1). They descend in the anterior or posterior parts of the internal capsule (2) and pass through the crura (3) and the mid-brain. The fronto-cerebellar are shown at (5); the temporo- and calcaro-cerebellar at (4). The fibres end at nuclei in the pons (6). Having relayed, the fibres proceed to the cerebellar cortex of the opposite side (8), either directly or *via* an intermediate relay in the vermis of the cerebellum (not shown).

FIG. 189. Cerebro-cerebellar (descending) Pathway for the Initiation of Group Movements. *N.B.*—The connections are crossed. (BAINBRIDGE AND MENZIES' "Physiology.")

(4) Head position sensations originating in the labyrinth travel as first order fibres to Deiters' nucleus; relaying here, they pass as second order fibres up the inferior cerebellar peduncle to end in the nucleus tecti in the base of the cerebellum. Here they probably relay once more to be distributed to the cerebellar cortex as third order fibres.

(5) Associated head and eye movements. This important function appears to be controlled by a group of nuclei which consists of the inferior olivary bodies, the superior corpora quadrigemina, the cervical segments of the cord and, probably, Deiters' nucleus. From all these situations, and particularly from the inferior olivary body, fibres pass in by the inferior cerebellar peduncle. They probably end in the vermis, whence fresh relays convey the impulses to the cerebellar cortex. From the cerebellum fibres probably proceed to the oculo-motor nuclei, and to the cervical segments of the cord *via* branches of the rubro-spinal tract.

FIBRES LEAVING THE CEREBELLUM. (1) The axons of the Purkinje cells travel as first order relay fibres up the superior cerebellar peduncles (*brachia conjunctiva*), crossing, as they do so, to the opposite side. They end in the red nucleus. Proceeding out of the red nucleus the second order relay fibres descend, and, crossing once more, get to the same side as that from which they started (Fig. 192). They descend in the rubro-spinal tract to the anterior horn cells. From here, third order relay fibres proceed to the muscles.

(2) The axons of other Purkinje cells travel to the nucleus dentatus; here second order relay fibres pass up the superior cerebellar peduncles; having decussated in the *brachia conjunctiva*, they ascend to the optic thalamus, where they end. From here, third order relays convey the impulses to the cerebral cortex (Fig. 191).

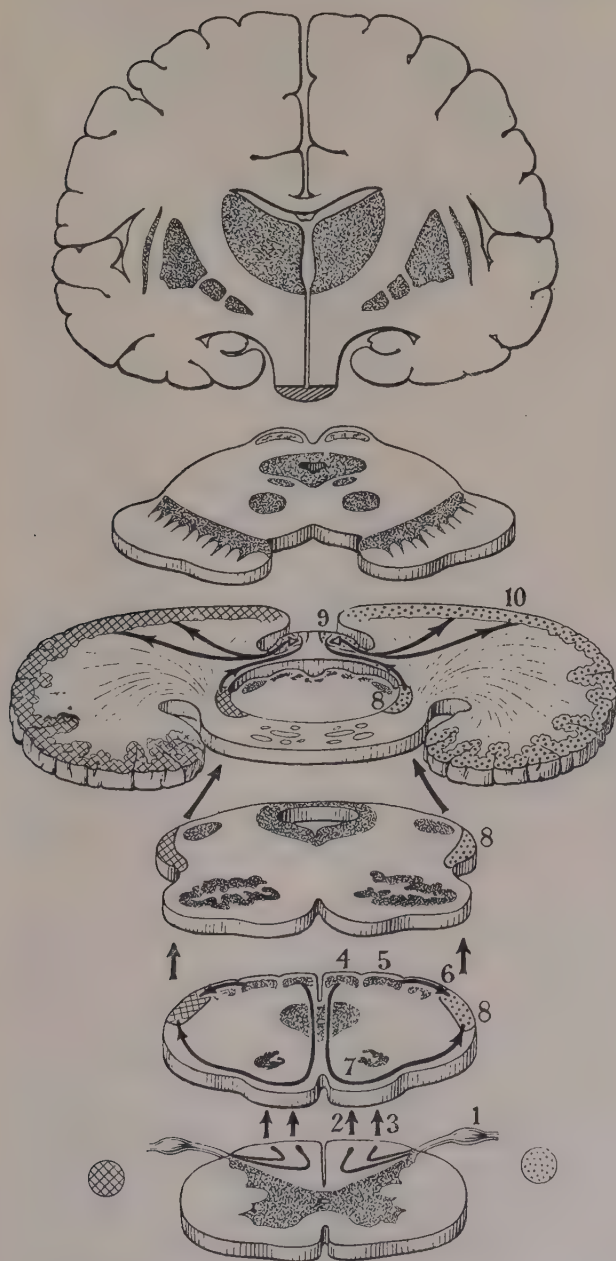
(3) From the cerebellar cortex fibres pass to Deiters' nucleus of the same side, passing out by the inferior cerebellar peduncle. Having relayed there, second order relay fibres descend in the vestibulo-spinal tract to the anterior horn cells of the cord, from which third order relay fibres convey the impulses to the muscles.

ABLATION OF THE CEREBELLUM IN ANIMALS. Various methods of investigating the cerebellum have been used by experimenters. The removal of the whole organ or of isolated parts and electrical stimulation have proved the most successful, and the effects of these experiments will now be described.

Unilateral extirpation of the cerebellum causes irritative effects, shown by jerking movements, for a certain time afterwards. These pass off, and the animal is then found to exhibit loss of tone and loss of power on the same side of the body. Thus, on attempting to stand, it falls over on the affected side. There is tremor in the affected muscles and willed movements are very clumsily carried out. Swimming is said to be better carried out than walking. Careful investigation of movements shows that they take a longer time than is normal, and that the muscle groups which usually work together do so in a clumsy manner, because there is not the proper give and take between antagonists. If the whole cerebellum is removed, the animal is unable to walk for several months afterwards. When it does so it makes its basis of support as wide as possible, and progresses by a series of springs, the two fore limbs and two hind limbs acting together. The diagonal movements of the fore and hind limbs are abandoned.

DESTRUCTIVE LESIONS OF THE CEREBELLUM IN MAN. In man the effects of loss of the cerebellum are usually very much less marked than they are in animals, so that congenital absence of this organ may lead

GROUP MOVEMENT CORRELATION



Path ascending to the cerebellum, conveying information from certain skin areas.

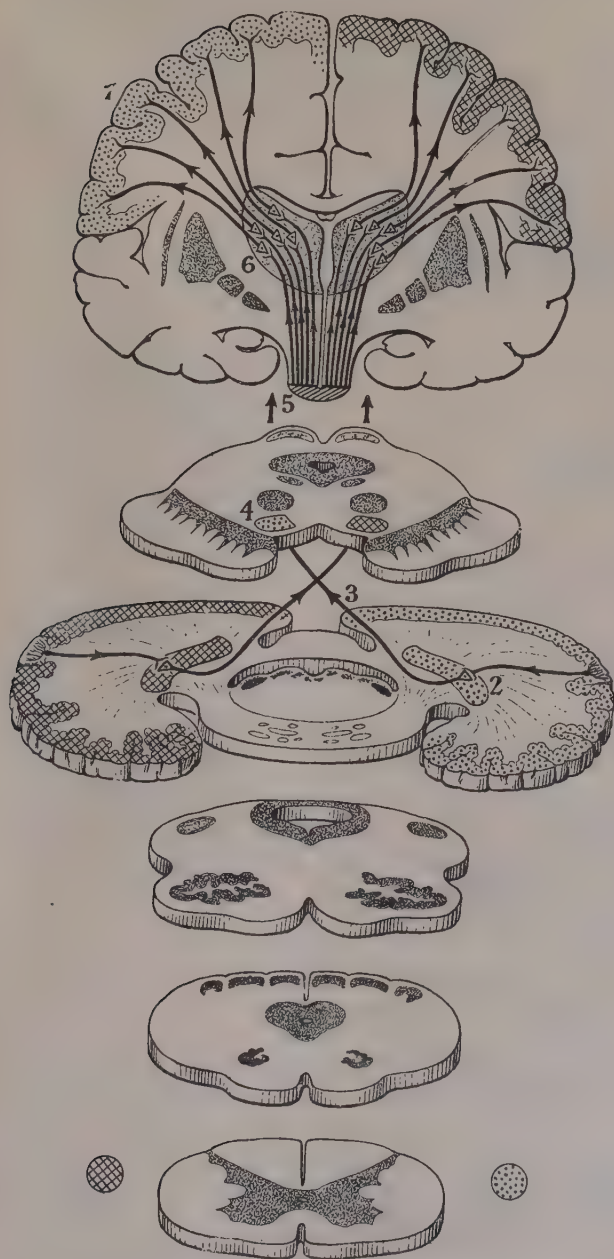
The fibres pass through the posterior roots (1) and enter the cord. They ascend in the posterior columns of Goll (2) and Burdach (3) to end at the Nuclei Gracilis (4) and Cuneatus (5). Having relayed, the fibres proceed as superficial (7) or deep (6) arcuate fibres to the direct cerebellar tract (8). By this they ascend into the inferior cerebellar peduncle to end at the vermis (9). Having relayed, the fibres proceed to the cerebellar cortex, conveying information from certain skin areas, *e.g.* the soles of the feet.

FIG. 190. Spino-cerebellar (ascending) Pathway for Impulses from Skin required for Group Control of Muscles. (BAINBRIDGE AND MENZIES' "Physiology.")

to no visible sign whatever. When the loss of the cerebellum, or parts of it, is due to disease there may be for some time afterwards signs which point conclusively to defects in the synergic control of the muscles. Thus, there may be (1) the asynergic gait, which is frequently described as resembling that of a drunken man. The body sways and there may be danger of falling towards one side, if one side alone is affected. Careful observation shows that the man is fully aware of his defect and makes most careful voluntary efforts to prevent himself falling or to minimise the harm that may result if he does do so. This is very different from the behaviour of a drunken man whose higher centres are even more inco-ordinated than the lower ones. (2) Asynergic movements. Careful observations of voluntary movements show that muscles which should co-operate in time and space do not do so; and further, the antagonist muscles which should exhibit the give and take necessary for the performance of the movement do not do this properly. If, for example, in a normal man the arm is voluntarily lifted from the table towards the face, the flexor muscles contract and the extensor muscles correspondingly relax, so that the hand rises smoothly. When it is a short distance from the face the flexor muscles cease to contract and the extensor muscles begin to contract instead, thus checking the movement and stopping the hand in the appropriate place. In cerebellar lesions this reciprocal action is lost, and the hand moves in a series of jerks. (3) Asynergic speech. Speech is frequently involved, the face and tongue exhibit jerky irregular movements, and the accurate timing of lips, tongue and larynx is lost. Speech is sometimes performed slowly, in the attempt to carry out the associations which normally can be effected quite speedily, or the affected man may try to hide his defect by accelerating the normal rate of speech. The result is what is called staccato or scanning speech. (4) Asynergia of eye movements. When the eyes are involved, the ability to perform normal fixation is lost, and in consequence the eyes make a series of rapid nystagmoid movements, no two movements being quite alike. A nodding of the head very frequently accompanies this. It seems extremely probable that some, at all events, of the symptoms which have just been described are due not so much to absence of parts of the cerebellum as to irritation, or unbalance by the disease, of the parts which remain. The fact that persons with congenital absence of a cerebellum exhibit no such defects as these would fit in with this hypothesis.

ELECTRICAL STIMULATION OF THE CEREBELLUM. Electrical stimulation of the cerebellar cortex has led to somewhat divergent views as to its function. There are certain points, however, on which all observers are agreed. Firstly, its function is one relating to the motor side of activity; secondly, stimulation always affects muscles on the same side of the body; and thirdly, its upper surface is related to the upper parts of the body and its lower surface to the lower parts. That is to say, the cerebellum is a paired organ, uncrossed and not inverted, the precise converse of the cerebrum. If suitable technique is employed, the effect of stimulating the cerebellar cortex electrically is to produce highly characteristic and sharply localised movements in collections of muscle groups. Figs. 193 and 194 show the results of such experiments. The weaker the electric stimulus used, the smaller is the group concerned; in fact it is even possible to produce isolated movements of the eyelids. The experimental removal of isolated parts of the cerebellum provides evidence which fits in extremely well with the results of electrical stimulation. There would seem to be no doubt, therefore, that in the same way that the motor area of the cerebrum represents in its different parts the different muscle groups of the trunk,

GROUP MOVEMENT CORRELATION

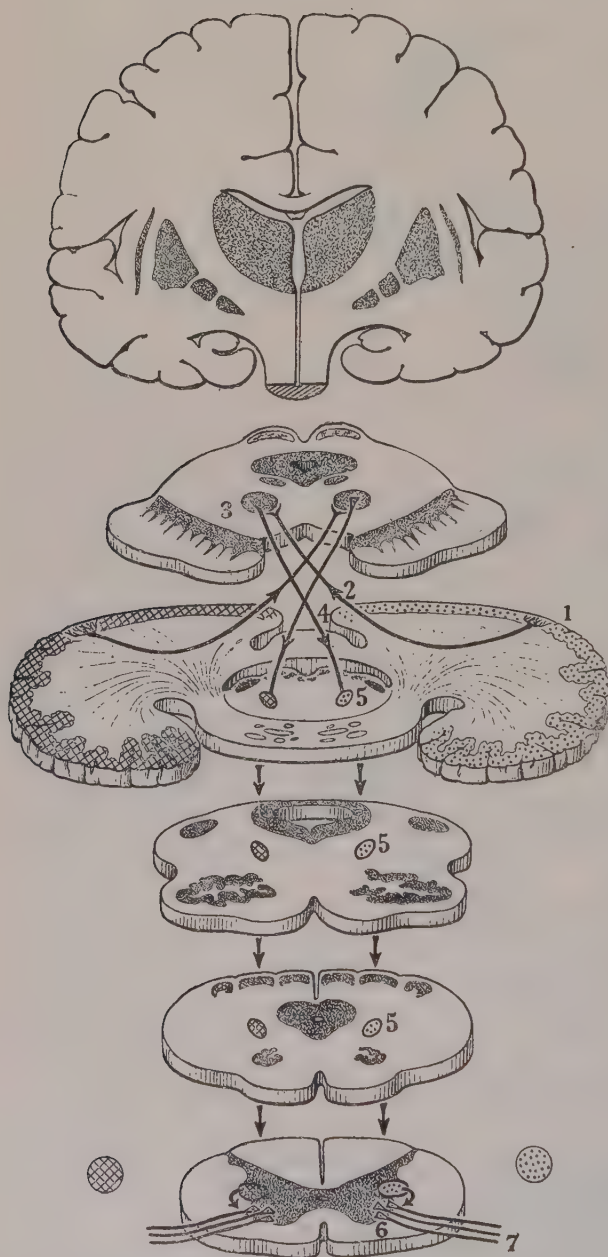


Path ascending from the cerebellum to the cerebral cortex, correlating their functions.

From Purkinje cells (1) the fibres convey the impulses to the Nucleus Dentatus (2). Having relayed here, the fibres convey the impulses up the superior cerebellar (Brachia conjunctiva) (3) to the opposite side. The fibres then proceed up the cerebello-thalamic tract (4 and 5) to the optic thalamus (6). Having relayed here, the fibres convey the correlating impulses to the frontal and post-central cerebral cortex.

FIG. 191. Cerebello-cortical (ascending) Pathway for Correlating the Functions of Cerebrum and Cerebellum. *N.B.*—The connections are crossed. (BAINBRIDGE AND MENZIES' "Physiology.")

GROUP MOVEMENT



Path descending from the cerebellum to the cord for the synergic (group) control of the muscles.

From Purkinje cells (1) the fibres convey the impulses up the superior cerebellar peduncle (2) (possibly relaying in the Nucleus Dentatus). They cross to the opposite side and go to the red nucleus (3). Having relayed, the fibres descend, crossing once more at (4), and descend in the medulla and cord as the rubro-spinal tract (5). The fibres turn off at various levels to go to the anterior horn cells (6). Having relayed, they go to the muscles for group movements, *via* the anterior spinal roots.

FIG. 192. Cerebello-rubro-spinal (descending) Pathway for Synergic (Group) Control of the Muscles. *N.B.*—The connections are twice crossed and therefore functionally homolateral. (BAINBRIDGE AND MENZIES' "Physiology.")

limbs, head, and neck, so also does the cerebellar cortex represent in a sharply defined and orderly manner those same muscle groups.

FUNCTIONS OF THE CEREBELLUM. We must now find a definition for the functions of the cerebellum. Whereas some of the older observers (Ferrier, Magendie) regarded the cerebellum as being primarily the organ for equilibration, Weir Mitchell, on the contrary, held the view that it was the centre for muscular energy. Luciani described the functions of the cerebellum in terms of his symptom triad: asthenia, atonia, and astasia (ataxia) following its removal. Recent observers, in particular Bolk and

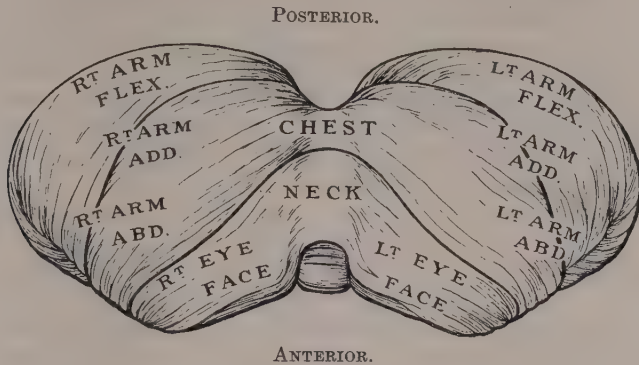


FIG. 193. Diagram of Upper Surface of Cerebellum, showing Cortical Localisation.
N.B.—The connections are uncrossed.

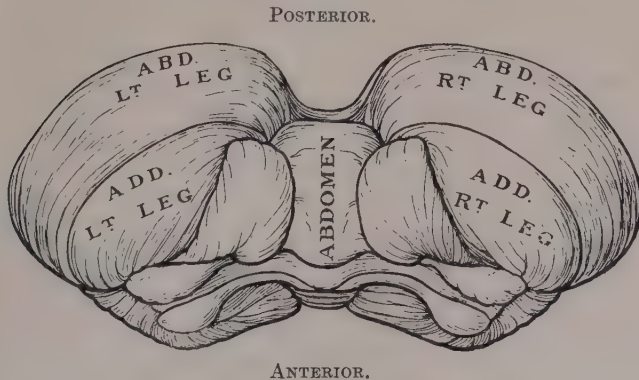


FIG. 194. Diagram of Lower Surface of Cerebellum, showing Cortical Localisation.
N.B.—The connections are uncrossed.

van Rijnberk, have emphasised the importance of synergic control, a view which also brings into line most of the older work. Not only is the cerebellum concerned with voluntary group movements, loss of which will produce weakness and inco-ordination of muscular effort, but it also concerns the highly important group-movements of muscles which together preserve equilibrium. We may define modern views with regard to cerebellar function in the following manner: suppose that we are commencing to learn the performance of some complicated motor act. We find at first that the control of the necessary movements is very difficult, but after a little practice and by great concentration we are able to perform the series of movements required. If we get tired or relax our attention for a moment this control fails, and the movements cease or become inco-ordinated. Gradually, how-

ever, proficiency is acquired. After a few days of practice we are surprised to find that our mind has been wandering and yet the skilled movements have gone on as well as before. We now find that our higher centres are behaving as if a tap was under their control. On turning this tap 'on' the complicated series of movements begins; on turning it 'off' the movements cease. What has probably been happening is that at first the movements of each muscle group had to be controlled by the concentration of the higher centres, but when once these had been arranged in an orderly manner, the cerebellum took over, a little at a time, the necessary group control of the muscles. When this state of affairs had been reached, it was merely necessary for suitable impulses of a simple nature to travel from the cerebrum to the cerebellum for the latter organ to send out, in its turn, streams of appropriate impulses affecting numbers of muscle groups. We may say, then, that the function of the cerebellum is to relieve the cerebrum of the necessity of giving detailed instructions for the carrying out of acts which are likely to be often repeated. It is natural that a great many of these acts should be directly or indirectly concerned with equilibration.

CHAPTER XX

HIGHER NERVOUS FUNCTIONS

1.—CONDITIONED REFLEXES

DURING the last twenty years Pavlov has introduced a new method for investigating the normal functions of the higher centres, which is capable of very wide applications, not only to the study of physiological problems, but also to pathology and pharmacology. It is not open to the same objections as older methods, since it is applied to perfectly normal animals, and affords means of observation of the effects and interaction of sensory stimuli. When used in combination with extirpation of different portions of the cortex it can be applied to the study of localisation.

THE UNCONDITIONED AND THE CONDITIONED REFLEX. All reflex activities can be divided into two large groups: *inborn*, and *acquired* reflexes.

The inborn reflexes are characteristic of the central nervous system of any whole class of animals: they are transmitted by heredity, and their formation is therefore independent of conditions under which any individual animal may live. Their strength may vary in the course of the animal's life: some of them do not appear until a definite age is reached, some disappear in senility, but in each case always to reappear in the next generation. To express the permanent stable character of these reflexes and their slight dependence upon surrounding conditions, Pavlov gave to the inborn reflexes the name of 'unconditioned reflexes.' All spinal and bulbar reflexes are unconditioned reflexes: the knee jerk, the stepping reflex, the secretion of saliva caused by administration of food, the flying reflex of birds, most of the postural, vascular and lower sexual reflexes, are included in the group of unconditioned reflexes. Some of these reflexes may be extremely complex and involve a series of successive reflexes, or be of an elaborate integrative nature, forming chains of reflexes following one another and presenting different groupings. What is generally known under the rather ill-defined name of 'instincts' is probably nothing but a very complex integration of these inborn or unconditioned reflexes.

The acquired reflexes are peculiar to a single individual animal and may be entirely absent from the rest of the individuals of the same class. They are acquired in the course of the animal's existence, as a result of adaptation to changes in the surroundings. The organism at birth presents merely greater or lesser possibilities for the formation of these reflexes, but their actual formation depends only on the conditions under which the individual animal lives. They disappear more or less quickly when the conditions of the animal's life become so changed that it has no more use for the previously acquired reflexes; instead of the lost ones it forms new reflexes. Hence the name given to them of conditioned reflexes. However, it is important to remember that the conditions of life among individuals of the same class of animals may be identical in many respects; therefore it is not surprising

that, besides possessing all the inborn unconditioned reflexes, these animals will also have many conditioned reflexes in common. The following example may serve as an illustration. Meat when placed into the mouth of any dog causes a reflex secretion of saliva and a reflex of deglutition. It is common knowledge that the same effects will also be produced if meat is only shown or given to smell. The latter reflex will be found just as universally amongst the carnivorous animals as the former. Food therefore, besides its property of causing these reflexes when directly stimulating the taste, can cause a similar effect through the optic and the olfactory nerves. Only by means of special experiments was it possible to show that secretion caused by the application of the stimulus to the taste buds is based on an unconditioned reflex, while that excited by the *stimulation of the visual and olfactory* receptors is a conditioned, *i.e.* acquired, reflex, and is common to all *carnivorous animals only because the conditions of their life are identical in respect of their food.*

THE FORMATION OF CONDITIONED REFLEXES. Conditioned reflexes never originate spontaneously. They only develop in association with another previously established reflex. In the simplest case conditioned reflexes are based upon an inborn reflex and, since conditioned reflexes are not hereditary, we must look upon all conditioned reflexes as being an associative development of the unconditioned inborn reflexes which ultimately lie at their root. Endless numbers of conditioned reflexes can be based upon one single unconditioned reflex. Conditioned reflexes of the second, third and higher orders can be developed in association with the primary conditioned reflexes, thus forming a complicated structure of nervous activities which are governed by education, experience and adaptation to the secondary conditions. The higher the animal's nervous system the greater the number and complexity of the conditioned activities it presents.

The experimental study of conditioned reflexes has dealt up to the present mostly with the simplest kind of reflexes which are developed in association directly with the unconditioned reflexes (conditioned reflexes of the first order). A stimulus which is quite neutral, in that it does not by itself originate any kind of reflex activity of the animal, when repeatedly used during the time an inborn reflex takes place (this latter of course in response to another stimulus), loses its neutral character and acquires the property of bringing about by itself the same result as the inborn reflex. The hitherto neutral stimulus is transformed into a conditioned stimulus: it acquires the properties of the stimulus which initiated the reflex, and this can now be set into operation not only by the unconditioned stimulus as before, but by another accessory stimulus.

An example will illustrate the point. It is well known that food or acid when placed in an animal's mouth causes a reflex secretion of saliva, which in a dog with a salivary fistula can be collected and measured. This is an inborn reflex, which does not require education, neither does it require the presence of the cortex, since it can be observed even after complete decerebration of the animal or even on a bulbo-spinal preparation. Now if a second stimulus, say a sound (or a tactile, visual or any other stimulus), is applied to the animal simultaneously with feeding and this combined stimulation is repeated several times, we find that the sound acquires stimulative properties and, when used alone without feeding, causes a secretion of saliva of the same character as does the food itself. A new reflex has thus been formed and a new nervous connection established. The sound in respect of the salivary gland becomes a signal for the food. Any other effector organ of the animal

besides the salivary gland, or any sort of stimulus, can be used for the establishment of conditioned reflexes. On account of the comparative simplicity of registering the reflexes the salivary glands have been most used as effectors. Conditioned reflexes have been established and studied also in the case of striated muscles, respiration, vasomotor system, pupil, deglutition, excretion of milk, contraction of the bladder, and intestinal and gastric secretion. It has been found possible to establish reflexes to visual, auditory, tactile, thermal, kinæsthetic, and olfactory stimuli.

RATE OF DEVELOPMENT OF CONDITIONED REFLEXES. Experiment shows that the development of conditioned reflexes is comparatively rapid. For example, a conditioned reflex was developed between the showing of food and the sounding of a note of 637.5 vibrations per second. The table shows that the reflex had nearly reached its maximum by the thirty-first repetition.

Number of repetitions of combined stimuli.	Strength of the conditioned reflex when sound tried alone. Drops per 30 secs.	Latent period of the secretion in secs.
—	0	—
9	18	15
15	30	4
31	65	2
41	64	3
51	69	2

Such a conditioned reflex as the above might be established quite quickly, that is within a few days, by repeating the combined stimuli of food and sound many times per day. When once such a conditioned reflex has been established evidence may easily be obtained for its existence for many years afterwards. If, however, the experiments be discontinued before it has been fully established the effects will be of a temporary nature. Suppose, for example, the above experiment had been discontinued on the ninth day, then, if tested on the fifteenth day, with no intermediate experiments, the probability would have been only a small secretion of saliva, indicating that the effect hitherto produced is fading away. If, on the other hand, experiments were continued until the fifty-first experiment, then a considerable effect might be obtained many months later.

GENERAL APPLICABILITY OF CONDITIONED REFLEX LAWS. Since the phenomena connected with conditioned reflexes are almost always investigated by means of some easily observed reflex act, such as salivation, the idea is apt to arise that conditioned reflexes only concern phenomena of this type; that, in other words, the whole subject deals with the very complicated mechanism of salivation. Such an idea is, of course, entirely erroneous. Such reflexes are chosen because by their use the observer has the best and most objective indication of what is happening in the animal's nervous system. The following example of a conditioned reflex which may bear no visible consequences whatever will therefore be given. A man is watching the house opposite, when he sees a big, burly man stop, ring the front door bell, and, a few moments later, enter. After the lapse of a few minutes, a small woman in black emerges, holding a handkerchief to her eyes. She disappears down the street in the opposite direction. If the observer saw this sequence of events happen once, or possibly twice, he would

think nothing whatever of it ; but if he had seen it happen every day at the same time for two or three weeks in succession, a conditioned reflex would be set up in his mind, and he would begin to think that the emergence of the crying woman was in some way connected with the entrance of the burly man. Since the observer does not salivate or give any other outward sign of what he is thinking, we could not form an opinion as to the nature or strength of the conditioned reflex which had been set up. Only by careful interrogation could we possibly judge it, and such interrogation is not possible when an animal is concerned. That is why in dealing with animals some easily observed act like salivation is used as an index.

SUMMATION. If, by means of separate applications, conditioned reflexes have been set up for two different kinds of stimuli, then on subsequently applying both of them together, double the effect may be produced which either would give alone. For example, suppose a conditioned reflex be set up by giving food and by sounding a whistle, and also in another series of experiments carried on at the same time, by giving food and stimulating the back electrically, then, if subsequently the electrical stimulation is given and the whistle sounded together, the number of drops of saliva will be found to be the sum of those given by either alone.

IRRADIATION. Suppose that a conditioned reflex be established for a carefully-marked area of skin, and that by testing this area the strength of the conditioned reflex be measured. If now a slightly different area of skin be stimulated, it will probably be found that the resulting flow of saliva is only a part of that obtainable if the correct spot had been stimulated. As spots further and further away from the correct one are tried, the number of drops decreases. A spreading of effect of this kind is called irradiation.

SPECIFICITY. Suppose that, having established a conditioned reflex for a particular gong, a gong of different pitch be sounded, then there may be either no flow of saliva or quite a considerable flow, according as the difference in pitch between the two gongs be large or small. This phenomenon is called specificity.

DISCRIMINATION. Suppose that a series of gongs of different pitch are obtained and that two of them be experimented with in the following manner. The sounding of gong A is always accompanied by the giving of food, whereas the sounding of gong B is not. Then on subsequently testing the animal for the existence of a conditioned reflex for these two gongs, it is possible to tell whether the animal has been able to distinguish between their pitches or not. Thus, if both of them are accompanied by secretion of the same number of drops of saliva on the average, then quite clearly they have sounded alike to the dog. By first testing with gongs which are very different in pitch, but in subsequent experiments using gongs which are closer and still more close, it is possible to ascertain precisely at what point discrimination ceases. Since very great care has to be taken to see that it is really nothing but the pitch which is the criterion that determines the dog's behaviour, tuning forks or organ pipes emitting pure tones will be preferable to gongs, and it would be necessary to be sure that no other quality changed at the same time, which would enable the animal to differentiate between them. Thus, one organ pipe might emit a slight high-pitched hiss when it was sounded, owing to a leak in its wind chest. This might be quite inaudible to us but easily discerned by the dog. We should think that the dog was discriminating between the tones by their pitches, while in point of fact it was discriminating them by the hiss in one of them.

REINFORCEMENT. Suppose that an animal in which a particular conditioned reflex has been established be put on one side for several months

and not experimented with, it will probably be found that the strength of the conditioned reflex has fallen somewhat from the value it had when the experiments ceased. This phenomenon is called decay. Experiment shows that a very few applications of the conditioning factors suffice to restore the reflex to its original value. This phenomenon is called reinforcement.

LINKING. Suppose that an animal with a conditioned reflex established between salivation and the sounding of a gong is experimented with for a few days by sounding a gong and a whistle at the same time. Then on subsequently testing the animal with the whistle it will be found that the conditioned reflex has a strength far greater than could be accounted for by the few times that the sound of the whistle and the feeding have been associated. What apparently has happened is that the conditioned reflex established for one sound has in great measure been transferred to the second. This phenomenon is called linking.

EXTINCTION. Suppose a conditioned reflex to have been established between the salivary reflex and the blowing of a whistle. Then, if for a number of times in succession the whistle be blown but no food given, it will be found that the strength of the conditioned reflex quickly dies away. This phenomenon is called extinction.

DELAYED AND TRACE REFLEXES. It is clear that the fundamental experiments with the modifications just described can be elaborated in a number of different directions. One of these consists in varying the time that is allowed to elapse between the application of the conditioned stimulus and the subsequent unconditioned stimulus. For example, the sounding of a gong and the giving of food may occur simultaneously, or any number of minutes may be allowed to elapse between the sounding of the gong and the giving of the food. If they occur together the conditioned reflex is called simultaneous. If some time is allowed to elapse between the two, they are called delayed, and if the time is several hours they are called trace reflexes. Now, as one would expect, delayed reflexes take longer to establish and are more liable to fade than simultaneous reflexes, and the same is still more true of trace reflexes.

Now it is clearly possible to vary the time between the sounding of the gong and the giving of the food in the opposite direction, namely, to give the food first and then to sound the gong. Experiment shows that unless the time be very short the establishment of a conditioned reflex becomes difficult or impossible. This is because the animal, as the result of repeated associations of the sounding of the gong and the giving of food, forms an association between the two, that is to say, the mechanism which sounds the gong is in some way connected with that which produces the food. If, on the contrary, the food is given first, so far as the animal is concerned subsequent events happening to the gong are of little or no interest. Perhaps another illustration may make the matter clearer. On looking out of the window one day, a big, burly man is seen to arrive at the house opposite, and a few minutes later a woman is seen to emerge in tears. On subsequent days, however, the woman hurries away from the house shortly before the man's arrival, and this continues to happen as long as observation is made. Evidently the conditioned reflex would not be set up in the observer's mind as the result of such events.

INHIBITION. EXTERNAL INHIBITION. Suppose that between the time of sounding the gong and the giving of food an additional unexpected stimulus be introduced, such, for example, as playing a gramophone record. Then it is found that this extra stimulus has a marked depressant effect on the strength of the conditioned reflex. The first application of this

unexpected stimulus has a more powerful depressing effect than subsequent ones, as the following table shows :—

Strength of visual conditioned reflex	.	.	.	=	100 per cent.
Effect of gramophone, 1st application	.	.	.	=	10 "
" " 2nd "	.	.	.	=	50 "
" " 3rd "	.	.	.	=	65 "
" " 4th "	.	.	.	=	85 "
" " 5th "	.	.	.	=	90 "
" " 6th "	.	.	.	=	94 "
" " 7th "	.	.	.	=	100 "

This effect is known as external inhibition. Experiments of this nature make it clear that considerable pains have to be taken to eliminate the entry of unintentional external inhibition when initiating or testing the strength of conditioned reflexes. It has been found necessary to design special rooms (Fig. 195) provided with automatic means of giving the animal food at the

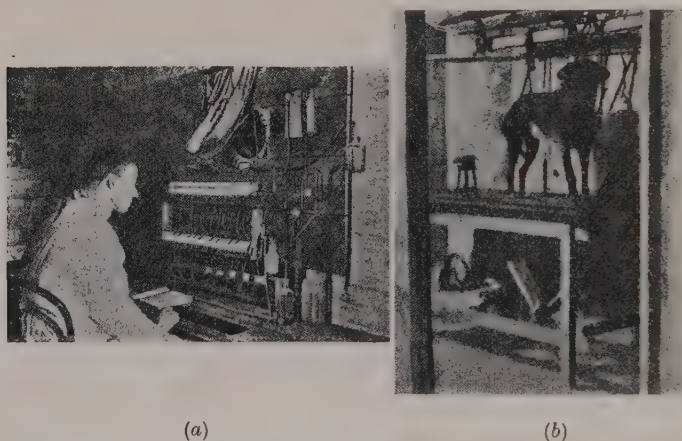


FIG. 195.—(a) Operator outside the cell observing animal by periscope; also shows the various controls. (b) The animal inside the chamber, (PAVLOV.)

required instant of time and for supplying the various forms of stimulation, gongs, whistles, &c., &c., so that adventitious stimuli of an unwanted kind are avoided so far as possible.

INTERNAL INHIBITION. Besides the type of inhibition described in the previous section, other varieties of inhibition are met with, some of which can be classed as internal inhibitions. For example, as the result of careful training a conditioned reflex may be set up for an organ pipe producing a note of 256 vibrations per second, whereas another similar pipe, producing a note of 244, is ineffective. In this case discrimination of the pitches of the two pipes has enabled the animal to react correctly to one and to inhibit the effects of the other. This is one type of internal inhibition.

EFFECT OF EXTERNAL STIMULI ON INTERNAL INHIBITION. We have already seen that adding an extra stimulus of an unexpected nature immediately before or after a stimulus to which a conditioned reflex has been set up may result in marked inhibition in the strength of the conditioned reflex. We must now consider the effects of putting an additional unexpected stimulus just in front of a stimulus to which internal inhibition has been established. For example, having caused the animal to discriminate between a tone of 256 to which he salivates, and another of 244 to which he does not,

let us investigate what will happen if, just prior to sounding the pipe of 244, an unexpected additional stimulus is given to the animal. The result is that the animal salivates as if it was responding to the tone of 256 vibrations per second, and this clearly indicates that the internal inhibition may be temporarily removed by this unexpected extra stimulus.

SEAT OF INHIBITION. We must now consider whether the inhibition which we have been considering develops primarily in the cortical area to which the normal stimulus goes, or whether it is associated more firmly with the cortical area to which the unexpected stimulus travels. Several observations seem to suggest that the inhibition arises within the cortical area to which the end organ concerned in the conditioned reflex connects. Suppose, for example, that as the result of repeatedly stimulating an area of skin and giving food, the conditioned reflex has been set up, and that a loud noise has been used to inhibit the conditioned reflex. Then experiment seems to show that the inhibitory after-effect will be much more marked in the cortical area representing the skin than in the cortical area representing hearing. The following experiment makes this clear. Suppose that a conditioned reflex has been set up for a particular area of skin, and that this has been inhibited by a loud sound so that the stimulation of skin only means to the animal to 'expect food,' whereas the loud sound and the stimulation of skin together mean 'no food.' Now, during a subsequent period another skin stimulus is used at the same spot for establishing a new reflex, for example, the contraction of a particular muscle instead of the secretion of saliva. Then, for the first time that the loud sound is applied at the same time as stimulation of the skin, there will be found to be inhibition of the movement of the muscle, just as there was inhibition of the flow of saliva. This clearly indicates that the association is between areas of cortex and not between the final paths used for the reflexes in question.

CONDITIONED REFLEXES OF HIGHER ORDERS. It is clear by using conditioned reflexes in various combinations, sometimes using the same stimulus for two different reflexes, sometimes using a stimulus which has been used to inhibit one reflex to bring about the operation of a second one, that we can link up conditioned reflexes in a very complicated way, only being limited by lack of time or of our own ingenuity. One example may be given. Suppose that a stimulus A be associated with the giving of food so that a conditioned reflex has been set up. Suppose that another stimulus B has been used to inhibit it, so that when A and B are being used together the animal realises that no food is coming. Suppose now that for several times in succession the inhibitory stimulus B is associated with a third stimulus C which the animal has not previously experienced. Then on trying A and C together it will be found that C inhibits just as effectively as B did. Suppose that to a small boy the village policeman is an inhibitory influence; then, if the small boy sees the village policeman in frequent company with a stranger in plain clothes, the inhibitory influence possessed by the policeman will be passed on to the stranger.

REMOVAL OF OR DAMAGE TO CORTICAL AREAS. Dogs which have survived the experimental removal of their cerebral cortex suffer a complete loss of the ability to form conditioned reflexes. Local damage only causes a temporary effect on conditioned reflexes if the damaged areas are of small size. Further, the damage appears to affect inhibitory stimuli more than excitatory ones. If, on the other hand, extirpation of the whole of the cortical area corresponding to a particular sense organ has been carried out, then all the effects previously produced by stimulating this sense organ are lost, no matter whether they were positive or negative.

HEREDITY OF CONDITIONED REFLEXES. One experiment to test this was performed as follows: Five puppies were removed from their mother and were fed entirely on milk. The first puppy had a conditioned reflex established between the giving of food and the sound of a metronome; the second puppy to the stimulation of the skin by an induction coil; the third to the smell of camphor; the fourth to the appearance of a red light; and the fifth to a white light, which periodically went on and off. The conditioned reflexes developed quickly, and on testing were found to be quite stable. When the puppies were several months old they were shown a number of different objects, amongst them being pieces of meat and other foods which their ancestors had been acquainted with. No salivary activity was observed in the puppies. It did not matter whether the animals were merely shown the objects in question or were allowed also to smell them. The results were the same. Meat and rubber corks alike were indifferent to them. We see, then, that the salivary reflex to sight or smell, which might be supposed to be a hereditary characteristic possessed by all dogs, is in point of fact an acquired conditioned reflex.

2.—SLEEP

When after a period of activity we feel tired, this may be caused by muscular fatigue due to the presence of breakdown products in our muscles, or it may be of nervous origin. Thus, muscle stimulated by its nerve until it is exhibiting fatigue, will contract vigorously again if the electrodes be placed directly on the muscle substance, showing that the fatigue has been produced, in part at all events, at the neuro-muscular junction. We are quite familiar with the nervous kind of fatigue after a hard day's mental work which has involved little or no muscular exertion. The symptoms are a feeling of heaviness in the head, a dryness of the conjunctivæ, and difficulty in keeping the eyes open. The temperature is found to be below normal, the respiration rate is reduced, so also is the pulse rate. Muscle tone is markedly diminished, reflexes take longer than usual, the thresholds for sight, hearing, and touch are above the normal, and reaction times are prolonged. Sometimes there is a feeling of coldness, extremities become numb, and shivering takes place. During sleep there is the same depression of all vital functions. Respirations are less frequent, deeper, and become less abdominal and more costal in type; if the eyes are observed it is found that the pupils are contracted and that the eye axes may be pointing in any direction. The blood pressure is low, the pulse rate is slow, the heart's output per beat small, muscle tone is poor, reflex actions are hard to obtain.

Two activities only are influenced by sleep, namely, (1) the secretory action of the skin, the fluid lost by the skin during one hour of sleep may be nearly as great as that produced during one hour of violent exercise; and (2) the rate of digestion. This fact has to be taken into account whenever it is necessary to determine the time of death from the time of taking the last meal.

The depth of sleep may be measured in a number of ways. The simplest is to take a record of the blood pressure, and to ascertain by experiment how loud a sound is necessary to cause a noticeable change in this. It is found that sleep increases in depth until, two or three hours after the onset of sleep, it reaches its maximum. After this it decreases until about six hours after the onset of sleep, and then stays approximately uniform. Just before the time to wake up is reached, it becomes very light.

As the result of experimental work on sleep, several hypotheses have been

advanced to explain it. One of these ascribes the phenomenon to the fall of temperature. In consequence of this fall the rate of all metabolic processes is diminished, reflexes take longer, the heart rate and the respiration rate are slowed, muscle tone is diminished, and the individual responds to this fall of temperature by shivering. The fall of blood pressure causes cerebral anæmia, and this in its turn causes a relaxation in the vaso-motor control of the vessels, and so a vicious circle is produced which causes the onset of sleep. This lowering of the temperature may be produced by an exhaustion of the local food stores, which are enabled to recoup themselves during the night. Other facts point, however, to the fall of blood pressure, and say that it is vascular failure which is responsible for sleep. This fits in with the fact that persons who have suffered a loss of blood feel drowsy and are prone to sleep for long periods.

Histological examination of the brains of animals which have been deprived of sleep for several days shows that there are marked changes in the nerve cells of the brain and spinal cord. The cells stain badly, there is chromatolysis, and the dendritic processes of the cells are retracted and knobby. Sometimes there are small hæmorrhages into the brain substance. Those physiologists who believe in the histological theory of sleep say that the increased resistance of the synapses caused by the withdrawal of the dendritic processes of the cells is really responsible for the phenomenon. In an unfatigued individual the synapse resistance is low, and the nerve impulses can pass freely from the dendritic processes of one cell to the next. When the same individual is fatigued the impulses find a far higher resistance offered to their passage. In consequence, thresholds rise, reaction times lengthen, muscle tone diminishes, the temperature falls, and the other phenomena of sleep follow.

The chemical theory of sleep rests upon the following evidence. If the cerebro-spinal fluid is removed from animals which have been purposely kept awake for many hours, and if this be injected into the cerebral cavities of normal rested dogs, it is stated that these exhibit the same urgent necessity for sleep that the other dogs exhibited.

Lastly, we must refer to Pavlov's theory of sleep. He showed that a phenomenon closely resembling sleep may be induced in animals by a spread of internal inhibitory processes. If, for example, an animal has been trained to expect food half an hour after an auditory stimulus has been given and that this time interval be made longer and longer, the animal tends to go to sleep during the intervening period. By performing a number of experiments of a similar kind on the same dog, the effects of these inhibitory influences may be summed, producing what is apparently perfectly normal sleep. When the time interval of the experiment is over the animal wakes up and exhibits the normal salivary reflex.

3.—SPEECH AND EXPRESSION

The development of the analytical powers of the auditory apparatus is closely connected with that of the faculty of speech, which is best considered with the central nervous system. We may first consider the mechanism of production of *voice*, which man shares with many other animals, before discussing the physiology of the wholly human faculty of speech.

Voice is produced in the larynx, a modified portion of the wind-pipe, by the vibrations of two elastic bands, the vocal cords, which are set into action by an expiratory current of air from the lungs. In many respects the larynx resembles a reed instrument, in which a current of air is caused to

vibrate by the vibrations of an elastic tongue. Whereas, however, the period of the vibrations in such an instrument, and therefore the note, is determined by the length of the tube which is attached to the reed and by the lengths of the reeds themselves, in the larynx the note produced by the blast of air is modified partly by alterations in the tension of the vocal cords, and partly by varying the strength of the blast of air.

ANATOMICAL MECHANISM OF THE LARYNX. The essential framework of the larynx is formed by four cartilages, viz. the cricoid, the thyroid, and the two

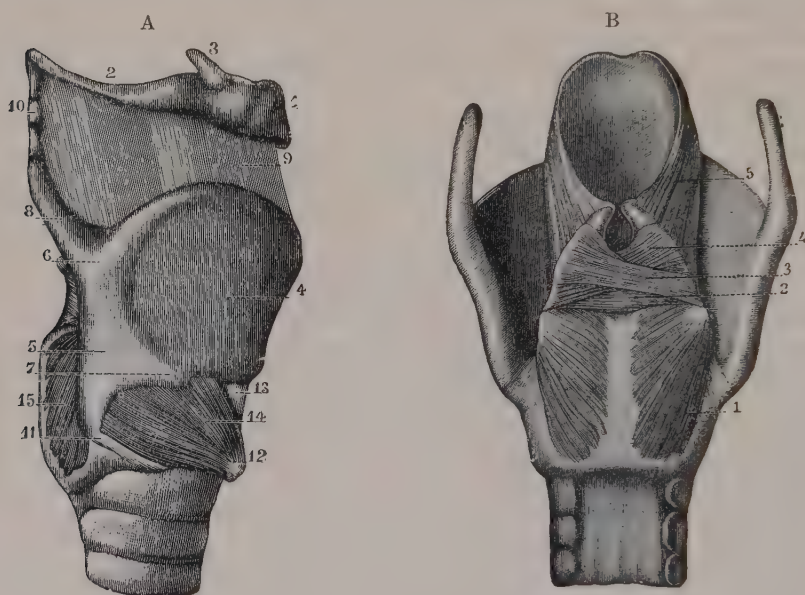


FIG. 196. Muscles of the Larynx. (SAPPEY.)

A, as shown in a view of the larynx from the right side.

- | | |
|---|---|
| 1. Hyoid bone. | 9. Thyro-hyoid ligament. |
| 2, 3. Its cornua. | 10. Cartilago triticea. |
| 4. Right ala of thyroid cartilage. | 11. Lower cornu of thyroid, articulating with the cricoid. |
| 5. Posterior part of the same separated by oblique line from anterior part. | 12. Anterior part of cricoid. |
| 6, 7. Superior and inferior tubercles at ends of oblique line. | 13. Crico-thyroid membrane. |
| 8. Upper cornu of thyroid. | 14. Crico-thyroid muscle. |
| | 15. Posterior crico-arytenoid muscle, partly hidden by thyroid cartilage. |

B, as seen in a view of the larynx from behind.

- | | |
|---|----------------------|
| 1. Posterior crico-arytenoid. | 2. Arytenoid muscle. |
| 3, 4. Oblique fibres passing around the edge of the arytenoid cartilage to join the thyro-arytenoid, and to form the aryteno-epiglottic, 5. | |

arytenoid cartilages (Fig. 196). The cricoid cartilage, which lies immediately over the uppermost ring of the trachea, is shaped like a signet ring, the small narrow part being directed forwards and the broad plate backwards. The thyroid cartilage consists of two parts or *alae*, joined together in front and forming the prominence known as Adam's apple; behind, it presents four processes or cornua, the superior of which are attached by ligaments to the hyoid bone, while the inferior cornua articulate with the posterolateral portion of the cricoid cartilage. By means of this articulation very free movement is permitted between the two cartilages, the general direction of movement being one of rotation of the cricoid cartilage on the thyroid, round a horizontal axis directly through the two articular surfaces between the two cartilages, while movements of the thyroid upon the cricoid are also possible in the upward, downward, forward, and backward directions. The two arytenoid cartilages are pyramidal in shape. By their bases

they articulate at some distance from the middle line with convex articular surfaces situated in the upper margin of the plate of the cricoid cartilage. The anterior angle of the base is the vocal process, while the external angle is the muscular process of the arytenoid. The crico-arytenoid joints permit of two kinds of movements of the arytenoid cartilages :

(1) Rotation on their base around their vertical long axis, so that the anterior vocal process is rotated outwards and the muscular process backwards and inwards or conversely.

(2) Sliding movements of the whole arytenoid cartilage either outwards or inwards, so that their inner margins may be drawn apart or approximated.

The larynx is covered internally by a mucous membrane continuous with that of the trachea. It is lined with ciliated epithelium, except over the vocal cords, where the epithelium is stratified. The two vocal cords, or thyro-arytenoid ligaments, consist of elastic fibres which run from the middle of the inner angle of the thyroid cartilage to be inserted into the anterior angle of the arytenoid cartilages. Their length in man is about 15 mm., in woman about 11 mm. The cleft between them is known as the glottis or *rima glottidis*.

Two ridges of mucous membrane above and parallel to the vocal cords are the false vocal cords (Fig. 197). Between the true and the false vocal cords on each side is a recess known as the ventricle of Morgagni. This ventricle permits the free vibration of the vocal cords. The false cords take no part in phonation, but help to keep the true cords moistened by the secretion of the numerous mucous glands with which they are provided. The false cords are also used in holding the breath. For this purpose they function in a similar manner to the mitral valve of the heart. It is found that animals, who need the thorax to be fixed in order that they may climb or strike, have well developed false cords. The position and tension of the vocal cords are determined by the action of the intrinsic muscles of the larynx. The part taken by the various muscles in each movement cannot be directly ascertained. We can in most cases study only the direction of the fibres and judge, from this direction and consequent isolated action of the muscles, the part taken by any given muscle in the production of voice. The chief muscles (Fig. 196) are the following:—

(1) The *crico-thyroid* muscle is a short triangular muscle attached below to the cricoid cartilage and above to the inferior border of the thyroid cartilage: the fibres pass from below upwards and backwards. When this muscle contracts, the cricoid cartilage is drawn up under the anterior part of the thyroid cartilage, so that its broad expansion behind, with the arytenoid cartilages, is drawn downwards and backwards, thus putting the vocal cords on the stretch. This muscle is probably the most important in determining the tension of the vocal cord.

(2) The *posterior crico-arytenoid* muscle arises from a broad depression on the corresponding half of the posterior surface of the cricoid cartilage. It passes upwards and outwards, its fibres converging, to be inserted into the outer angle of the arytenoid cartilage. These muscles rotate the outer angle of the arytenoid cartilages backwards and inwards. They thus cause a movement outwards of the anterior angles, so that the glottis is widened. During every act of inspiration there is a widening of the glottis, which is probably effected by contraction of these muscles. If they are paralysed the vocal cords are approximated and tend to come together during inspiration, so that dyspnoea may be produced.

(3) The *lateral crico-arytenoid* muscle arises from the upper border of the cricoid cartilage and passes backwards to be inserted into the muscular process of the arytenoid cartilage. These muscles when they contract pull the muscular process of the arytenoid cartilage forwards and downwards, thus approximating the vocal cords at their posterior ends and antagonising the action of the posterior crico-arytenoid muscles.

(4) The *arytenoid* muscles consist of transverse fibres, some of which decussate, uniting the posterior surface of the two arytenoid cartilages. When they contract they draw the arytenoid cartilages together.

(5) The *thyro-arytenoid* muscles consist of two portions. The outer fibres rise in front from the thyroid cartilage and pass backwards to be inserted into the lateral border and the muscular process of the arytenoid cartilage. Some of the fibres pass obliquely upwards towards the aryteno-epiglottidean folds. These are often spoken of as a separate muscle, the *thyro-epiglottidean*. By their action they tend to draw the arytenoid cartilages forwards and to relax the vocal cords. The upper fibres may also assist in depressing the epiglottis. The inner fibres are called the *musculus vocalis*. They arise from the lower half of the angle of the thyroid cartilage, and, passing backwards in the vocal cords, are attached to the vocal processes and to the adjacent parts of the outer surfaces of the arytenoid cartilages. Many fibres do not run the whole distance, but end in an attachment to some part of the vocal cord. Although their

action must be to draw the arytenoid cartilages forwards, yet, since they are contained in the vibrating portion of the vocal cords, they cannot by their contraction relax these cords. It is probable that they play a great part in determining the tension of the vocal cords after these have been put on the stretch by the action of the crico-thyroid muscles. They may possibly act as a sort of fine adjustment of the tension, the coarse adjustment being represented by the crico-thyroids.

THE PRODUCTION OF VOICE

In order to study the changes in the larynx which are associated with voice production, we must make use of the *laryngoscope*. The principle of this instrument is very simple. A large concave mirror with a central aperture is fixed before one eye of the observer, sitting in front of the patient or person to be observed. The latter is directed to throw his head slightly backwards and to open his mouth. In order to keep the tongue out of the way the patient is made to hold the end of it by means of a towel. The mirror is then so arranged as to reflect light from a lamp into the cavity of the mouth. A small mirror fixed in a handle is then warmed, so as to prevent the condensation of the patient's breath, and passed to the back of the mouth until it rests upon and slightly raises the base of the uvula. By this mirror the light reflected into the mouth from the large mirror is again reflected down on to the larynx, and a reflection of the larynx and trachea is seen in the mirror.

By laryngoscopic examination we can see the base of the tongue, behind which is the outline of the epiglottis. Behind this again in the middle line are seen the two vocal cords, white and shining (Fig. 197). The cords appear to approximate posteriorly; between them is a narrow chink, the diameter of which varies with each respiration, being wider during inspiration. On each side of the true vocal cords are seen the pink false vocal cords. In some cases the rings of the trachea, and even the bifurcation of the trachea itself (Fig. 197, c), may be seen in the interval between the vocal cords.

In order that the vocal cords may be set into vibration, they must be put into a state of tension, and the aperture of the glottis narrowed so as to afford resistance to the current of air. In the dead larynx it is possible to produce sounds by forcing air from bellows through the trachea, after the vocal cords have been put on the stretch by pulling the arytenoid cartilages backwards. By experimenting on patients on whom tracheotomy has been performed, it has been found that the pressure of air in the trachea, necessary to cause production of voice, is, for a tone of ordinary loudness and pitch, between 140 and 240 mm. of water, and with loud shouting the pressure rises to as much as 945 mm. of water. This pressure is furnished by the contraction of the expiratory muscles, *i.e.* of the abdomen and of the thorax. Since the pitch of the note produced rises with increasing force of the blast, while the tension of the cords remains constant, it is evident that, in the act of 'swelling' on a note, the increased pressure necessary for the crescendo must be associated with diminishing tension of the cords. It is the failure to secure this muscular relaxation that so often causes a vocalist to sing sharp when swelling on any given note.

The voice, like the sound produced on any musical instrument, may vary either in pitch, loudness, or in quality or timbre. The range of any individual voice is generally about two octaves. The pitch of the voice usually employed is determined chiefly by the length of the vocal cords. Thus in children the voice is high-pitched. Before and at puberty there is a considerable development in the size of the larynx in both sexes. This

is especially marked in the male, and accounts for the sudden drop in pitch ('breaking') of the voice. In the female the greater size of the larynx is chiefly perceptible in the increase in fulness and richness of the voice which occurs at this age. Even when we take all the voices together, bass, tenor, alto and soprano, the total range for ordinary individuals does not exceed three octaves. In singing, the voice may be produced in various

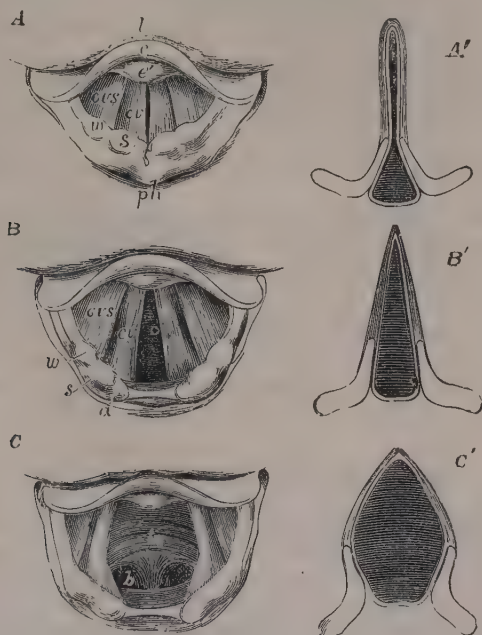


FIG. 197. Three Laryngoscopic Views of the Superior Aperture of the Larynx and surrounding parts in different states of the Glottis during life. (From CZERMAK.)

A, the glottis during the emission of a high note in singing.

B, in easy or quiet inhalation of air.

C, in the state of widest possible dilatation, as in inhaling a very deep breath.

The diagrams A', B', C' have been added to Czermak's Figures to show in horizontal sections of the glottis the position of the vocal ligaments and arytenoid cartilages in the three several states represented in the other Figures. In all the Figures so far as marked, the letters indicate the parts as follows: *l*, the base of the tongue; *e*, the upper free part of the epiglottis; *e'*, the tubercle or cushion of the epiglottis; *ph*, part of the anterior wall of the pharynx behind the larynx; in the margin of the aryteno-epiglottidean fold *w*, the swelling of the membrane caused by the cuneiform cartilage; *s*, that of the corniculum; *a*, the tip of the arytenoid cartilages; *cv*, the true vocal chords or lips of the rima glottidis; *cus*, the superior or false vocal cords; between them the ventricle of the larynx.

In C, *tr* is placed on the anterior wall of the receding trachea, and *b* indicates the commencement of the two bronchi beyond the bifurcation, which may be brought into view in this state of extreme dilatation.

ways, *i.e.* in different registers. Thus we distinguish the chest register, the middle register and the head register. The deeper notes of any individual voice are always produced in the chest register. Observation of the vocal cord shows that when producing such notes the glottis forms an elongated slit, all the muscles which close the glottis and increase the tension of the cords being in action. The vocal cords are relatively thick and broad and can be seen to vibrate over their whole extent. When singing with the head voice, the vibrations of the cord are apparently confined to their inner margins; the aperture of the glottis is wider in front than behind, so that

more air escapes during phonation by this method than in the production of the chest voice.

In order to change the pitch of the note the following means are probably employed in the larynx :

- (1) Alteration in the tension of the vocal cords.
- (2) Alteration in the length of the part of the vocal cords that is free to vibrate, which can be accomplished by the approximation of the arytenoid cartilages to one another, or by their approximation to the thyroid cartilage.
- (3) The alteration in the shape of the vocal cords, which is determined by the activity of the different portions of the internal thyro-arytenoid muscles.
- (4) The varying pressure of the blast of air passing through the glottis.

The loudness of the tone produced is practically proportional to the force of the blast of air employed. The quality or timbre of the voice depends not so much on the vocal cords as on the accessory resonating apparatus, represented by the trachea and chest and by the cavities of the mouth and nose. The greater part of the education involved in voice training is directed to the modification of the shape of the mouth cavity, so as to secure the greatest possible fulness, *i.e.* richness in overtones, of the tone produced in the larynx.

THE MECHANISM OF SPEECH

The sounds employed in speech, *viz.* vowels and consonants, are produced by modifying the laryngeal tones by changes in the shape of the mouth and nasal cavities. In whispering speech there is no phonation at all, but the sound is produced by the issue of a blast of air through a narrow opening between the lips, between the tongue and soft palate, or between the tongue and the teeth.

VOWEL SOUNDS are continuous, whereas the consonants are produced by interruptions, more or less complete, of the outflowing air in different situations. The simple vowel sounds, U, O, A, E, I (pronounced as in Italian *oo, oh, ah, eh, ee*), are tones, *i.e.* are produced by a regular series of vibrations. These tones take their origin in the mouth cavity, as can be shown easily by the fact that we can whisper these sounds distinctly without any phonation whatever. To each of them correspond one or two distinct notes, the pitch, *i.e.* the resonance, of which is regulated by the shape of the cavity in which they are produced. There has been much controversy as to whether the pitch of these notes changes at all with the pitch of the voice, or varies in different individuals. Some said that they did not change, others that their pitch kept in constant ratio with the pitch of the note sung : if the note doubled in pitch, so also did that (or *those* in the case of E and I) of the vowel. Several methods have been employed for investigating this point :

(1) By recording the vibrations emitted by the voice by means of the manometric flame.

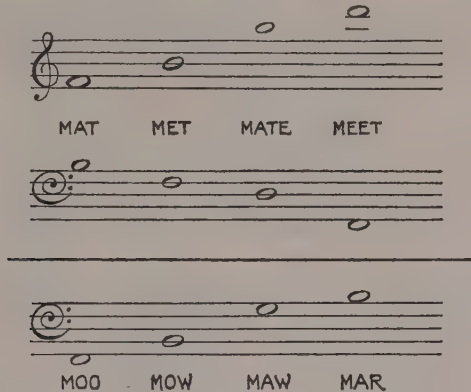
(2) By analysis of the vibrations recorded by means of a gramophone.

(3) By measuring the intensity of vibration of series of resonators. All the above methods show that there must be some change, even if it is slight.

(4) By running a gramophone record of a bass voice at an increased speed so that the notes were those of a treble. If now the pitches of note and

vowels were in constant ratio, the quality of the vowels should not change when the speed is thus increased. Experiment shows that the words are greatly altered, losing their O's and A's and taking E and I instead. This shows clearly that change in pitch of the vowels is not nearly as great as that of the note sung with them. We must conclude therefore that neither those who say there is no change, nor those who say there is constant ratio, are right, but that the truth lies between the two extremes. The pronunciation even of the simplest vowel sounds differs in different individuals. For instance, those pronounced by a Londoner differ from those pronounced by a man from Manchester or from Yorkshire, and the French vowels differ somewhat in pitch from those employed by the German, and these again from those employed by the average Englishman.

The characteristic notes are as follows :



If the five vowels are whispered loudly, the gradual rise in pitch of the tone is easily perceptible. We do not in this way, however, note the lower component of the sound in the E and I; this can be brought out by a simple device (Fig. 198). If we place the mouth in the position necessary to produce these different vowels, and then percuss over the cheek, we obtain the typical note for each vowel, the air in the mouth cavity being set into vibration by the percussion. Now shift the finger which is to be percussed, so that it lies over the pharynx just behind the angle of the jaw, and percuss again. The note will be observed to rise with U, O, A and then fall with E, I. With the three vowels U, O, A, we have a single cavity formed by the lips, the palate and the tongue; this cavity is longest and narrowest with U and shortest and most open with A. With E and I the dorsum of the tongue comes up against the front part of the soft palate, so that the mouth cavity is divided into two, the anterior short narrow cavity, and the posterior broader cavity between the soft palate and the base of the tongue. We therefore have two notes produced, one in each cavity. The change in shape of the mouth cavity is shown in the Figures. With U and A the cavity seems to be single; with I the development of a pharyngeal resonating cavity is well shown. Diphthongs are produced by changing the form of the mouth cavity from that of one vowel sound to another, thus AI (the English I) = ah-ee run together and abbreviated.

CONSONANTS are sounds produced by a sudden check being placed in the course of the expiratory blast of air by closure of some part of the pharynx or mouth. They are classified into labials, dentals, or gutturals, according as the check takes place at the lips, between teeth and tongue, or between back of tongue and soft palate. Each of these again can be divided into

soft and hard consonants as they are accompanied or not by phonation. Thus when we pronounce D the production of the laryngeal sounds goes on during the check of the sound produced at the teeth, whereas with T there is an absolute interruption of phonation during the pronunciation of the consonant. It is thus practically impossible to make any marked difference between hard and soft consonants when whispering.

In the production of nasal sounds such as NG, the mechanism is the same as for the production of B, D, G, except that the posterior opening of the nares is not kept shut by the soft palate, so that part of the sound comes continually through the nasal passages, when it acquires a peculiar resonance. These sounds are on this account often spoken of as 'resonants.' The aspirates are produced by the passage of a simple blast of air through a narrow opening which may be at the throat as in H, between tongue and teeth as in TH, or between lips and teeth as in PH or F.

The vibratives, such as R, are formed by placing the tip of the tongue, or the uvula, or the lips, in the path of the blast of air so that they are set into

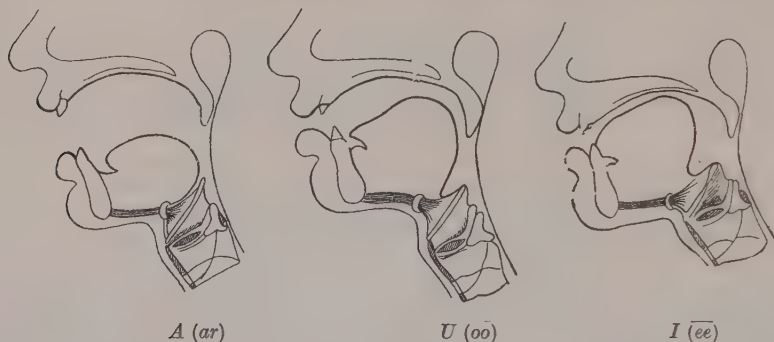


FIG. 198. Shape of the Oral Cavity in the production of the Vowel Sounds, A, U, I. (GRÜTZNER.)

vibration by the blast. In English the vibrative R employed is entirely due to the tongue.

The sibilants, which may be voiceless, as in S, or accompanied with phonation, as in Z, consist of continuous noises produced by a narrowing of the path of the air between the tongue and the hard palate. They are therefore similar in production to the aspirates. In the production of the sound L, the tongue is applied by its edge to the alveolar process of the upper jaw, so that the air or voice escapes by two small apertures in the region of the first molar and between the inner side of the cheek and the teeth. The acoustic characters of these various consonants are still but imperfectly studied.

THE NEUROLOGY OF SPEECH

The intricate function of speech involves the employment of three different mechanisms: (a) The lungs, (b) the larynx, and (c) the cavities of the pharynx, mouth and nose. The lungs develop the necessary air pressure. The vocal cords of the larynx set the air into vibration with the required pitch. The cavities above, *e.g.* the mouth, modify the intensity of the tone and the relative intensities of its overtones so as to produce words.

THE LUNGS. For purposes of respiration the lungs are alternately filled and emptied by the synchronous action of two sets of muscle fibres,

those of the chest wall and those of the diaphragm. In addition, the muscles of the abdomen and arms and neck may be called into play when occasion demands more thorough ventilation. These muscles are innervated by nerve fibres which originate in the cells of the anterior horn of grey matter in the spinal cord corresponding to all thoracic segments. Details of this innervation will be given in the chapters on respiration. These same muscles are synchronously brought into play for purposes of phonation by voluntary impulses which, for a time, replace the normal respiratory rhythm. In general, inspiration is quickened, the vocal cords are separated, and air pours into the lungs. The vocal cords are now brought together and put under tension. Expiration now begins, and air commences to pass between the cords; these vibrate, producing sounds which are modified into speech. Expiration is prolonged until we have completed the sentence. The expiratory pressure even in quiet speech is above that during ordinary respiration, while in shouting not only the ordinary expiratory muscles are forcefully contracted, but the accessory muscles of expiration (*e.g.* the abdominal) are freely made use of as well. Considerable muscular effort is required for loud speech or song. So great may it be that the individual becomes breathless as he does when performing other kinds of severe muscular effort.

THE MUSCLES OF THE MOUTH, &c. There are six points at least at which modification in diameter of the air cavities above the vocal cords may be produced: (*a*) The false cords innervated by the recurrent laryngeal branch of the vagus, or tenth cranial nerve; (*b*) the pharynx at the level of the root of the tongue, pharyngeal branch of vagus; (*c*) the buccal cavity near its posterior part, by the elevation or depression of the soft palate, by the spinal accessory or eleventh cranial nerve; (*d*) the buccal cavity near its middle, by the elevation or depression of the dorsum of the tongue, by the hypoglossal or twelfth cranial nerve; (*e*) the buccal cavity near its front by the approach of the tip of the tongue to the upper teeth; (*f*) the buccal cavity at its anterior outlet by the approximation of the lips (facial or seventh cranial nerve).

In addition, the mouth cavity may be varied in size by the change in angle of upper and lower jaw (trigeminal, fifth cranial, nerve), and the nasal cavity may be allowed to communicate with the pharynx at its posterior outlet (spinal accessory or eleventh cranial nerve).

We may summarise these nervous controls by saying that the seventh, tenth and twelfth cranial nerves play the principal part in controlling this mechanism of speech.

THE CORTICAL CENTRES OF SPEECH. At one time it was thought that there was a definite motor area for speech. It was called Broca's area after its discoverer, and occupies the posterior part of the inferior frontal gyrus. In right-handed people it is found on the left side of the brain only, and *vice versa*. Destruction of this area undoubtedly causes dumbness, but histological evidence shows that it is an association area only. After destruction of this area the lungs can still be voluntarily ventilated. The cords can still be approximated and set into vibration, the false cords, pharynx, tongue, and lips, can all be separately moved, but the complex correlation of all these separate motor functions is no longer possible. We may say, then, that, as the result of external stimuli, impulses reach Broca's association area, and by it they are distributed in suitable combination to the motor cortex of lips, tongue, cords, diaphragm, &c. The impulses travel down the axons of the Betz cells thus innervated, through the corona radiata, internal capsule, mid-brain, and pons, to reach either directly or through intermediate connections the motor nuclei of the seventh, tenth, and twelfth

cranial nerves, and the anterior horn cells of the spinal segments involved in the act.

Broca's area is by no means the only important cortical association area involved in speech; others are found near both the auditory and visual cortex.

APHASIA. It has been usual to divide the disorders of speech, known as aphasia, into the following groups: (1) motor aphasia of Broca; (2) sensory aphasia of Wernicke; (3) alexia; (4) anarthria. A more fundamental idea of the processes involved will, however, be obtained if it is remembered that there are two ways in which the necessary ingoing impressions are received, namely, by reading written or printed words and by hearing spoken words. There are, correspondingly, two different mechanisms by which speech may be caused to emerge, namely, by writing and by speaking. Consideration of these facts would suggest that there may be eight possible different defects: (1) vision may be perfect and yet there may be complete inability in understanding written or printed words (alexia); (2) hearing may be perfect and yet the man may be incapable of understanding what is said to him (this is called sensory aphasia of Wernicke); (3) he may be able to use his hands and to draw with a pencil and yet be unable to write (agraphia); (4) he may be able to use his lips and to make noises with his throat and yet be unable to speak (anarthria or motor aphasia of Broca). Each of the above defects concerns one particular mechanism alone. Other possible defects may concern two mechanisms, one ingoing and one outgoing. Thus (5) there may be ability to read with inability to copy what is read, or (6) ability to read but inability to read aloud, or (7) ability to understand what is spoken but inability to write it down to dictation, or (8) ability to understand what is spoken and yet inability to repeat it.

The neurological basis of language must be regarded as co-extensive with the sensory centres, and with the whole region of lower association. We might speak of auditory and visual word-centres as located in the visuo-psychic and auditory psychic centres. There is probably, however, no word, still less a collection of words, expressing an idea which does not involve the activity of practically all parts of the cerebral cortex. As Bolton points out, "a word, such as 'mouse,' at once sets in effect processes of association which pass to every projection sphere with the solitary exception of the gustatory, and even this may be aroused in a person who has eaten a fried mouse in the hope of thereby recovering from an attack of whooping-cough." The amount of impairment of intelligence will vary in different cases according to the extent of the lesion. Thus, softening affecting the occipital lobe may, with hemianopia, cause 'word-blindness' or 'alexia,' a loss of power of appreciating the meaning of written words. In most individuals and certainly in the uneducated, this power may be cut out altogether without interfering considerably with the mental powers. On the other hand, from babyhood upwards we have learnt the meaning of words and their grouping by auditory impressions. If the whole of the auditory associations be destroyed by an extensive lesion in the first and second temporal convolutions, the resulting loss of word appreciation, sensory aphasia, will be attended with great diminution of mental powers. It must be remembered that the area of Wernicke is not a sensory centre, but a centre of association between the various sense impressions, especially those of hearing and sight. It may therefore be spoken of as an intellectual centre. Pure motor aphasia, if it exists, is always anarthria and is due to a lesion in the lenticular zone, *i.e.* in the lenticular nucleus and its neighbourhood, in the anterior part and the genu of the internal capsule and possibly in the external capsule.

THE FUNCTION OF EXPRESSION. Although we rightly give precedence to speech as a means of conveying our ideas to one another since it is extremely exact, other modes of expression are of considerable interest since they probably once played a more prominent part than they do at the present day. No attempt will be made here to analyse them in detail. They may be divided anatomically into facial, manual, corporal, and pedal. The first comprises all those movements of expression of the superficial muscles of the face, the lips, the jaw, tongue, etc., which are called into play. Thus, corrugation of the superficial muscles of the forehead indicates surprise or worry; if the eyebrows are raised at the same time it indicates surprise; if they are lowered it indicates anger. The orbicularis muscles of the eyes when relaxed show astonishment or interest, and when contracted indicate boredom. Tremor of the lids expresses extreme mental agitation. The lips may be pursed up to show doubt, spread out in a smile, or separated in a grin.

Manual expressions are not so easily analysed as the above, but may be divided arbitrarily under a time, space, and intensity distribution. For example, the placing of the first finger on the lips to give the order for silence; patting the hands quietly together to signify approval; the slow raising and lowering of the right hand, palm downwards, to signify go slowly or stop. The conductor of an orchestra will show many examples of the expressions which come under this category.

Corporal expressions, for example, leaning forward in a chair when interested, or leaning back when bored, or crouching as if to spring when in disagreement with what is being said, or when angered with the speaker.

Pedal expressions, for example, the shuffling of the feet when the mind is anxious, or the stamping of the foot when angry.

All the above are under the control of the will. In addition, there are the factors controlled by the sympathetic system which are not under voluntary control, namely, the erection of the hair (the hair 'stands on end'), the dilatation of the pupil, and the activity of the sweat glands. Stimulation of the lachrymal glands expressing sorrow, and the cessation of the secretion of the buccal glands when the mouth becomes dry accompanying an anxious state of mind.

CHAPTER XXI

THE NERVOUS MECHANISM OF POSTURE

1.—HEAD POSTURE

WHEN the posture and movement of animals are studied the importance of head position is easily established. This may be regarded from two aspects: (a) The orientation of the head with regard to the vertical and horizontal planes; and (b) the position of the head with regard to the trunk. Detailed consideration will be given later to experiments which demonstrate these facts.

THE NORMAL HEAD POSITION. Under normal circumstances at least three mechanisms contribute to preserve the orientation of the head in what is called the 'normal' position, that is, with a horizontal line joining the centres of the eyes (this can be estimated with great precision) and with the eyes and the occipital protuberance lying in the same horizontal plane (this description refers to man; it cannot be measured with great precision, and probably does not apply to animals.) These three mechanisms are: (a) Vision; (b) the sensations from the vestibular organs; and (c) the kinæsthetic sensation from the neck muscles.

(a) **VISION.** In man and most animals (rabbits and guinea-pigs appear to be exceptions) the eyes play a very important part in head orientation, and it is quite easy to see how this is effected, for on rotating the head about a sagittal axis the horizon appears to tilt at a corresponding angle in the reverse direction. Corresponding angle does not mean the same angle, because of the phenomenon of compensating eye rotation. That is, the rotation of the eyeball, as a whole, which is effected principally by the superior and inferior oblique muscles, tends to compensate for the head rotation, thus tending to preserve the image on the retina in its normal position. In man compensating rotation is very defective and, therefore, the rotation of the image on the retina can be used for head-righting purposes. In rabbits, in which the compensating rotation is very complete, the retinal image can obviously be no index of head rotation, for the simple reason that on rotating the head the eyes perform a compensatory rotation and thus the retinal image does not alter. The orientation of the head about a lateral axis, *i.e.* a tilting of the head forward or backwards, is detected partly by a change in the retinal image and partly by kinæsthetic sensations from the muscles and tendons of the eyes. For example, suppose the head to tilt forwards, a compensatory upward tilt of the eye axes (levator palpebræ, superior recti and inferior obliques) will preserve the direction of the gaze. The greater part of the retinal image will be the same as it was, but a change will have occurred in the peripheral field, for the eyebrows which, with the head in its normal position, cut off the upper portion of the visual field, will now cut off more of it. But in the lower part of the visual fields the obstruction of the cheeks will have become correspondingly less. These changes in the periphery of the retina therefore act as indexes of deviations of the head from

the normal position. The kinæsthetic sensations from the eye muscles will also be different from what they were before. The superior recti and inferior obliques and the tendons attached to them are in greater tension, and the inferior recti and superior obliques, and their tendons in less tension than in the normal positions. The kinæsthetic sensations thus aroused are accessory to the retinal ones.

The importance of visual judgments in such animals as cats and dogs can be easily demonstrated. For if by surgical interference the labyrinthine sensations are eliminated, then a few days later the animals are found to be able to orientate their heads quite well. This, however, ceases to be the case if their eyes are bandaged.

The nerve paths concerned are therefore (a) the optic nerves conveying impulses from the retina, and (b) the kinæsthetic impulses from the extrinsic eye muscles, which probably travel with branches of the trigeminal (fifth cranial) nerve. All the optic nerve fibres concerned terminate in the calcarine cortex, and the impulses thus reach consciousness. Other fibres

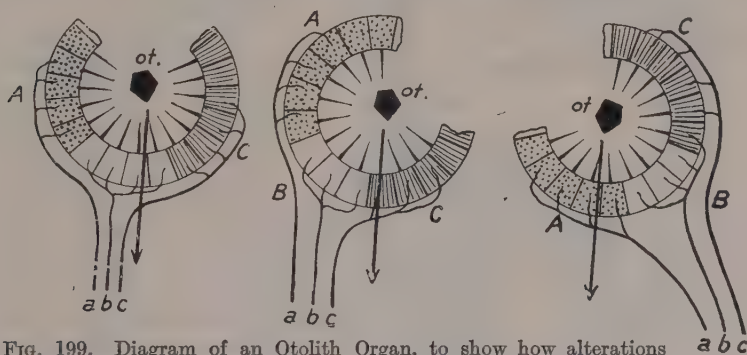


FIG. 199. Diagram of an Otolith Organ, to show how alterations in its position will cause the weight of the otolith (*ot.*) to press on different sense cells, and therefore to affect different nerve fibres.

relay the impulses by the temporo-calcarine cerebellar tract to the cerebellum for synergic eye, head and trunk movements (Fig. 179).

The kinæsthetic impulses also partly travel to the post-central sensory cortex for conscious appreciation of eyeball position and partly travel to the cerebellum for synergic control.

(b) THE LABYRINTH. The primitive auditory sac arises as a simple involution of the surface. In the course of development the anterior part is modified to form the canal of the cochlea, which is set apart entirely for the reception of sound. From the posterior part there are formed two sacs—the saccule and utricle—and the three semi-circular canals. The saccule and the utricle, which receive each a large branch of the vestibular nerve, represent the *otolith organ*, which is found in almost all classes of animals. The crayfish *Palæmon* has, for instance, at the base of its antennæ a small sac lined with hairs and richly supplied with nerves. In this sac a small calcareous particle rests on the hairs. It is evident that the incidence of the pressure of the small stone or otolith on the hairs will vary according to the position of the animal (Fig. 199), so that any change in the position of the head will be attended by alteration in the nerve fibres which have been stimulated by the pressure of the otolith, and therefore in the nature of the impulses flowing to the central nervous system.

The importance of these impulses in regulating the locomotion and the maintenance of the equilibrium of the animal is well shown if the otolith be

replaced by a small fragment of iron. Under normal circumstances the iron particle will act quite as well as an otolith. If however a powerful magnet be brought in the neighbourhood of the animal the pressure of the particle will not be determined simply by gravity and therefore by the position of the animal, so that there will be discordance between the impulses arriving from the otolith organ and those arising from the other sense organs of the body, and marked disorders of equilibrium will be the result.

In mammals that part of the labyrinth which represents the primitive otolith organs consists of a bony framework containing perilymph, in which is contained the membranous labyrinth. The osseous labyrinth consists of a cavity, the vestibule, into which open behind the three bony

semicircular canals. In the vestibule are contained two little membranous sacs, the utricle and saccule, the cavities of which are connected by means of the *sacculus endolymphaticus*.

Into the utricle open the three semicircular canals, the three canals having five openings. These semicircular canals are arranged in three planes, each of which is at right angles to the other two, so that in the organ are represented the three planes of space. We may distinguish on each side an external or horizontal canal, an anterior or superior vertical canal, and a posterior vertical canal. The two outer canals lie always exactly in the same plane, which in the normal position of the head is practically the horizontal. Each posterior vertical canal lies in a plane which is parallel to that of the superior vertical

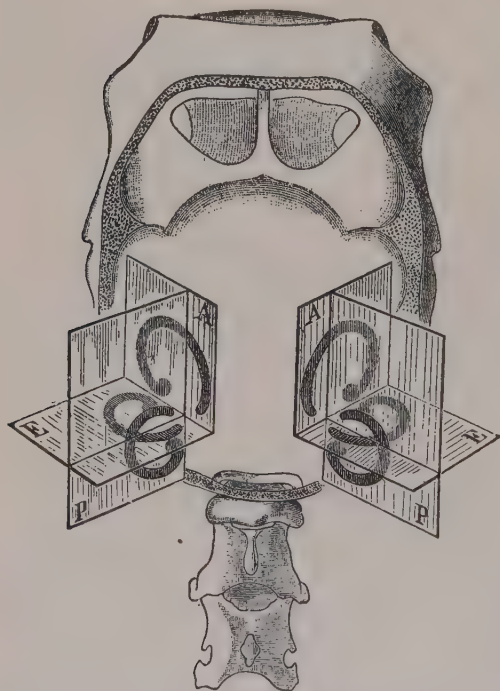


FIG. 200. The situations of the Semicircular Canals in the Skull of the Pigeon. (EWALD.)

canal of the opposite side. We thus see that these semicircular canals form together three planes, one horizontal and two vertical, the two latter being at right angles to one another (Fig. 200). The membranous canal lies within the osseous canal, a considerable space intervening between the two canals. At one end the osseous canal is dilated and the membranous canal undergoes a corresponding dilatation so as to fill up the whole bony canal. In this dilatation, which is known as the *ampulla*, we find the ending of a branch of the vestibular nerve in a special sense epithelium forming the *crista acustica* (Fig. 201). The crista is composed of hair cells with sustentacular cells between them. The fibres of the vestibular nerve end in arborisations among the hair cells, the hairs of which project into the endolymph filling the ampulla.

In the utricle and saccule we also find special sense organs, known as the *maculae acusticae*, the structure of which is very similar to that of the

crista in the ampullæ. Among the hairs of the macula, however, are found numerous small concretions of carbonate of lime, the otoliths.

Since the nervous apparatus of the labyrinth is not excited by changes in the environment, from which it is carefully shielded, but by changes in the animal itself, we are justified in assigning it to the proprioceptive system, of which indeed it represents the most important receptor. The changes which arouse impulses from the labyrinth are those affecting the orientation of the head when at rest, with respect to gravity, *i.e.* in space, and movement of the head; and the use of these impressions is to determine the posture and movements of the animal as a whole.

THE FUNCTIONS OF THE VESTIBULAR ORGANS. The most usually accepted hypothesis is that the macular (otolith) organs are con-

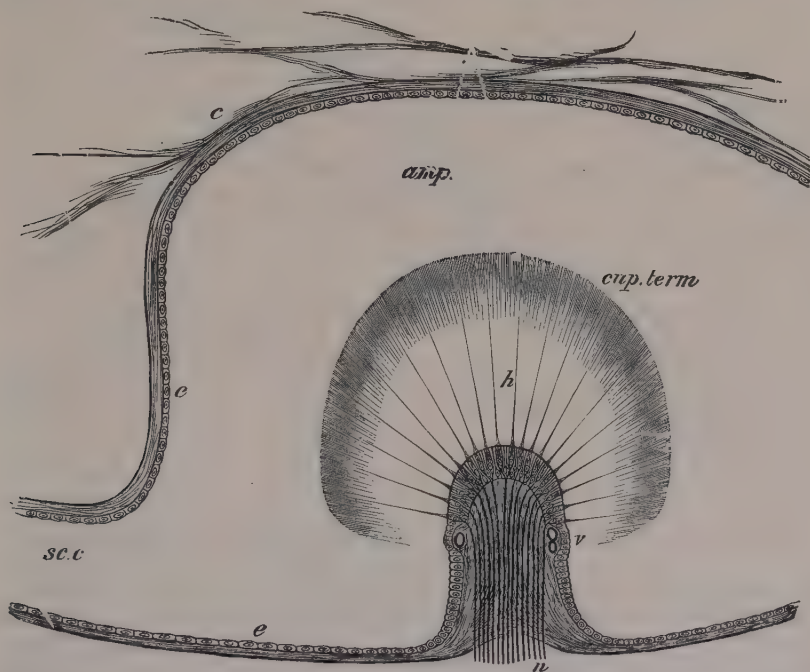


FIG. 201. End Organ of Vestibular Nerve in Ampulla of Semicircular Canal ('Crista Acustica').

cerned with the positions of the head, while the ampullæ of the semicircular canals are concerned in notifying movements, particularly rotations. Whereas the former are static organs, the latter are kinetic. Two views have been held about the otolith maculæ: (a) That bending of the hairs causes stimulation; (b) that pulling on the hairs does so instead. Two views have similarly been held about the semicircular canals: (a) That each canal operates in one direction of rotation only; (b) that each canal operates in two directions of rotation opposed to one another. Thus, according to the first, on rotating the head about a vertical axis so that the nose moves to the left, there is stimulation of one horizontal canal. If the nose moves to the right, the other horizontal canal is stimulated. According to the second theory each horizontal canal is stimulated by both rotations but in contrary senses. Again some have held that pressure of the liquid on the hairs in the ampullæ brings about stimulation. Others think that it is the bending of the hairs

which is the essential factor. Suppose, for example, the head were suddenly rotated about a vertical axis, the nose moving to the right. The walls of the horizontal canals will rotate in the same direction. But the contained fluid remaining stationary owing to inertia will tend to apply forces to all structures with which it is in contact. The hairs in the ampullæ will then have a force applied to them tending to bend them, like reeds in a flowing stream. Whatever these details may be, all the above minor hypotheses have accepted the main hypothesis that maculæ respond to positions and the canals to rotations. But against the main hypothesis have been advanced the following objections: (a) that the canals have bores far too fine for any streaming of fluid to take place; (b) that if the otolith concretions of the maculæ

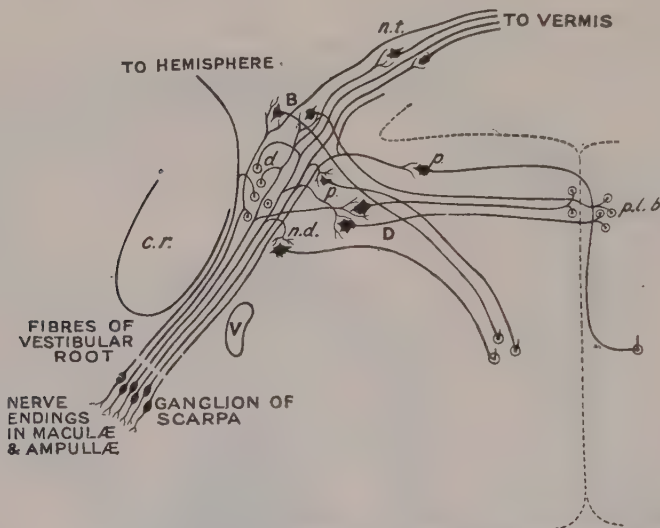


FIG. 202. Plan of the Course and Connections of the Fibres forming the Vestibular Root of the Auditory Nerve. (SCHAFER.)

c.r., restiform body; *v*, descending root of fifth nerve; *p*, cells of principal nucleus of vestibular root; *d*, fibres of descending vestibular root; *n.d.*, a cell of the descending vestibular nucleus; *n.t.*, cells of nucleus tecti (fastigii) of the cerebellum; *pl.b.*, fibres of posterior longitudinal bundle. No attempt has been made in this diagram to represent the actual positions of the several nuclei. Thus a large part of Deiters' nucleus lies dorsal to and in the immediate vicinity of the restiform body.

possess mass they must also possess inertia. If gravity can act on them, so also can moment of inertia, and hence they should be affected not only by static positions, but also by rotations. These are admittedly weighty objections against the current theory, and it seems that while it is clear that the vestibular organs give the higher centres important information as to the position and movements of the head, it is not clear how they do this.

NERVE PATHS CONCERNED. The vestibular part of the eighth cranial nerve enters the pons above the cochlear division. It passes between the inferior cerebellar peduncle and the descending spinal root of the fifth cranial nerve. Its fibres end by arborising round one of four different collections of nerve cells. These were once designated as a whole as 'Deiters' Nucleus.' Now, however, this name is applied to the lateral group only. Fibres originating in these nerve cells convey impulses which cause movements of the eyes, neck, and trunk; in addition, large numbers of them go

to the cerebellum. Some details concerning these connections will now be given.

Fibres conveying impulses to the eye muscles run principally from the superior vestibular nucleus ('Bechterew's N.'). Some, however, go from the lateral vestibular nucleus ('Deiters' N.'). Their effects are of two kinds, those produced on a normal man or animal while he is being rotated, and those produced on a man or animal after he has been rotated so as to produce giddiness. The normal movements are of such a kind that the gaze remains fixed on external objects during the rotation until they pass too far outside the field of view. The eyes now make conjugated movements of an extremely rapid nature in the same direction as the rotation until once more fixation of the gaze is effected on external stationary objects. Once more the eye performs a slow rotation in the opposite direction from that in which the man is rotating, so that in this way the fixation is preserved. Then the quick movement follows. The rotations of the eye are therefore slow ones in the opposite direction to the rotation of the man and quick ones in the same direction. These movements are called *nystagmus*. These movements may be very beautifully observed by rotating on ball-bearings a platform, at the centre of rotation on which is placed a chair on which the subject sits. Opposite him, and at one edge of the platform, is mounted a cinema camera so that a continuous picture is taken of his head and eyes. If now the rotation is continued for several minutes, nystagmus gradually dies away and external objects form images which move over the retina, no attempt being made on the part of the man to scrutinise them. If when the subject has become giddy, the rotation of the platform is suddenly stopped the cinema camera records precisely the opposite nystagmus to that which was recorded at first. If the slow movement on commencing the motion was to the right and the quick one to the left, it is a slow movement to the left and a quick one to the right which is now recorded, and the man's sensations are that he is now being rotated in the opposite direction to that at which he was being rotated at first. That is to say, his eyes are producing the appropriate nystagmus to correspond with the sensations which he is perceiving.

Fibres conveying impulses to the cerebellum run principally from the lateral vestibular nucleus (Deiters' N.), enter the inferior cerebellar peduncle and are distributed to the vermis of the cerebellum from which third order relays take them to its cortex. Fibres conveying impulses to the neck and trunk travel by two separate routes, the vestibulo-spinal tract and the Deitero-spinal tract. The latter consists partly of crossed fibres, but most of them are uncrossed. They end at cells near the anterior grey matter of the cord in the cervical, thoracic and lumbar regions, either directly or with an inter-connecting relay. They are concerned with those movements of the trunk and neck which will cause the head to take up and enable it to retain its normal position. Suppose, for example, an animal to be laid on its side. It will first rotate its head until it is held in the normal position. Then, holding the head in this position, the thorax will be rotated until it too is held in the normal position, *i.e.* with the shoulder blades on a horizontal line with one another. Lastly, the hind quarters will be rotated so that they occupy the normal position. The animal is now in the correct position for getting up when it wishes to do so. It should be noted that the first thing that occurs is the placing of the head in its normal position. Throughout the succeeding movements which take place this position of the head is retained.

(c) **KINÆSTHETIC NECK SENSATIONS.** In addition to the head-

position sensations from eyes and labyrinth, two different kinds of sensations originate in association with the neck : (A) those concerned with the poise of the head, and (B) those concerned with the position of the head relative to the trunk.

A. Head Poise. As the head is changed from an inclined position to the normal position, the tension in the neck muscles producing the elevation progressively diminishes until in the normal position the head almost balances without effort. A slight action of the muscles, now to right, now to left, now behind, now in front, suffices to preserve its poise. The kinæsthetic sensations in the neck muscles, ligaments, and joints, are important because they help in this poising of the head in the normal position with the minimum of effort. This state of poise can be effected with the head rotated to right or left, or with the trunk leaning forward or back.

B. The Position of the Head relative to the Trunk. The importance of this lies not, as might be supposed, in helping to give us information concerning the position of our heads, that of our bodies being known, because such a sequence happens but rarely. On the contrary, it is almost always used to give information as to the positions of the body, that of the head being already known by means of the sensations specified above.

It has been stated that sensations from the vertebra prominens, or the skin over it, contribute important sensory impressions, on the evidence that pressure here diminishes extensor tonus in all four limbs, causing the animal to crouch. It is not difficult to explain this. The vertebra prominens is sharp, and pressure over it causes pain, to avoid which the animal reflexly crouches.

The nerve paths concerned in these kinæsthetic neck sensations are similar to those for kinæsthetic sensations from other muscles, joints, bones, etc., of the body ; the chief is that ascending in the posterior columns of the cord ; the fibres relay in the nucleus cuneatus, and second order relays proceed from here, crossing to the opposite side in the sensory decussation of the medulla to form a part of the mesial fillet which ends at the optic thalamus. From here, third order relay fibres convey the sensations to the post-central sensory cortex. Other fibres proceed from the neck muscles and convey impulses which relay in the vermis of the cerebellum from which they are conveyed to the cerebellar cortex of the same side. This enables the cerebellum to correlate these sensations with the others which are poured into it and which are utilised for the correct association of muscle group movements.

The following experiment will emphasise the importance of normal head position. With the eyes open and the head and body in a normal position the individual does his best to walk along a straight chalk line drawn on the floor. He should have not the slightest difficulty in doing this. Now, voluntarily inclining the head well towards the left (or right) he attempts to repeat the performance. It will probably be found that he has very much greater difficulty in doing this than he had before. In a second experiment, with eyes shut, the subject can walk in a fairly straight line, but with the head held to one side such a feat becomes almost an impossibility.

2.—BODY POSTURE

One of the characteristic reactions of an intact animal is its ability to stand in the erect position in opposition to the pull of gravity. Very simple experiments demonstrate the fact that, strange as it may seem, the higher parts of the central nervous system are not involved in such a postural reflex. Thus, after decerebration, either alone or combined with removal of the cerebellar hemispheres, instead of this tone in the extensor muscles being

diminished, it is actually increased (Fig. 203*b*). If we make sections at other levels of the central nervous system in our attempt to find out which are the essential parts concerned, we find a region at or below the red nucleus to be the important controlling centre. For example, a decerebrate preparation which shows marked extensor tone loses this tone if a section is made below the red nucleus (Fig. 203*a*). In consequence of experiments done on these lines, the red nucleus itself, or Deiters' nucleus, or some nucleus in this neighbourhood, has been supposed to play the major part in controlling posture.

THE NERVE PATH INVOLVED. If the anterior nerve roots be destroyed, there is, of course, an immediate disappearance of tone from the muscles supplied, but the same thing is also true of cutting the posterior nerve roots. This would indicate the importance for postural tone of impulses which are entering the spinal cord. If, now, in another preparation the columns of Goll and Burdach are cut, the postural tone is again lost, indicating that this is the route by which these impulses travel. Now, impulses entering at the posterior roots travel towards higher parts of the brain by relaying in the nuclei gracilis and cuneatus, crossing in the sensory decussation, and thus ascending in the lemniscus. This cannot be the fate



FIG. 203. (a) Decapitated cat, no postural reflexes. (b) Decerebrate cat showing decerebrate rigidity, or exaggerated reflex standing. (c) Thalamus rabbit (cerebrum removed), pose normal. (MAGNUS.)

of the fibres under consideration, as is shown by the fact that cutting the lemniscus above the level of the red nucleus does not affect postural tone. The fibres concerned must, therefore, have turned off, probably soon after they have relayed in the nuclei gracilis and cuneatus. It is possible that some of the superficial and deep arcuate fibres are concerned. They may travel, for example, to Deiters' nucleus to be correlated there with impulses coming in from the vestibular organs, as the result of which impulses descend to the lower spinal segments by means of the vestibulo-spinal tract.

THE STRETCH REFLEX. The phenomenon on which our present knowledge of postural reflexes is founded is that of the stretch reflex of Sherrington. In a decerebrate animal the limb muscles exhibit tone which can be measured by suitable means; by isolating a particular muscle, and by connecting it to isometric recording levers, the amount of its tone can be readily measured. If now additional force is applied to the muscle so as to attempt to elongate it against the tonic pull which it is exerting, the immediate result is a very great increase in the tonic contraction. In other words, the muscle resists stretching, and this phenomenon is called the stretch reflex. Experimental investigation shows that the mechanism to which this reflex is due is of a very simple nature. The initial tonic contraction in the muscle stimulates the sensory end organs inside that muscle. In consequence, kinæsthetic (proprioceptive) impulses travel up from the sensory

end organs to the posterior roots of the cord, and so by short reflex arcs the anterior horn cells of the muscle are stimulated, thus keeping up the initial tone observed. If, now, a force tending to overcome that tone is applied to the muscle the stimulus to the sensory end organs is very greatly increased, and in consequence kinæsthetic impulses of a much stronger character pass to the posterior roots, setting up in their turn more powerful impulses from the anterior horn cells and a more powerful contraction from the muscle. The attempt to stretch such a muscle by three or four millimetres may result in a ten- or twenty-fold increase in the strength of its tonic contraction.

CONDITION IN A POSTURING LIMB. If we examine in detail the different muscles concerned, and particularly if we ascertain the effect of applying a force to the limb so as to introduce stretch reflexes, then we should expect from the above experiment to find certain muscles initially in contraction to exhibit greatly increased tone. Thus, on moving the limb in such a way that a stretch is applied to the extensor muscles, the extensor tone greatly increases, so keeping the limb in the extended position. If now we turn our attention to the antagonistic flexor muscles, we should expect to find them flaccid, since movements of the limb which would tend to set up stretch reflexes in the extensors might be expected to have the opposite effect on the flexors. Such, however, is not the case. We find, on the contrary, that the flexors are in contraction, though not to the same extent as the extensors. This flexor tonus is explained by the effect of the pressure on the sensory end organs of the skin, for not only is the pressure on the pad of the foot tending to set up stretch reflexes in the extensor muscles; it is also causing kinæsthetic sensations to pass from the sensory end organs in the skin of the foot and more deeply placed tissues, and from these impulses are travelling to the cord to add their effects to those of the stretch reflexes.

THE NERVE SEGMENTS INVOLVED. There is another and more fundamental difference between the mechanism involved when a muscle exhibits the stretch reflex phenomenon, and that concerned either in the whole limb, when both flexors and extensors are in tonic contraction, or in the animal as a whole when exhibiting postural tonus, namely, the number of spinal segments involved and the complexity of the whole nerve mechanism. There is conclusive evidence that in the case of the single muscle exhibiting the stretch reflex one spinal segment alone may be involved. It appears to be possible by stretching the individual parts of which a big muscle may be composed to put them separately into the condition of tonus, without the intervention of the other parts. On the other hand, when by pressure on the sole of the foot both extensors and flexors are set into tonic contraction, several, or even many, spinal segments may be involved in the reflex. Further, when the posture of the animal as a whole is considered, we find that much more than the mere number of segments appertaining to the different limbs in question is involved. In order that the animal shall exhibit the modifications in posture which are brought about by kinæsthetic sensations from the neck and from the vestibular organs, it is necessary that it should have, in addition, the higher controlling centre, the location of which we considered earlier in this section.

INFATIGUABILITY OF POSTURING MUSCLE. Liddell and Sherrington were the first to draw attention to the fact that muscles in tonic contraction exhibited very little evidence of fatigue. Subsequent investigators went so far as to say that the oxygen consumption in an animal exhibiting decerebrate rigidity was practically identical with that in which the

muscles were flaccid. Such, however, is not quite the case. In Fig. 204 are shown the oxygen consumption and CO_2 output in animals before and after the abolition of decerebrate rigidity. On the average, the tonically contracted muscles increase the oxygen utilisation and CO_2 output by about 25 per cent. This is, of course, very much less than would be consumed by the same muscles if they were in tetanic contraction. The explanation of this moderate increase in oxygen requirement and CO_2 output is that a portion only of the muscle fibres are in contraction at any one moment. This function of contraction the different fibres take on in rotation. While one set contracts the others are at rest, each fibre contracting in an all-or-nothing manner, the number in contraction at any one moment depending on the tension to be developed. It must not be thought that a muscle, exerting one-tenth the greatest contraction of which it is capable, has muscle fibres one-tenth of which are in contraction, and that then this tenth stop contracting and a fresh tenth enter into contraction, and then they stop and a further

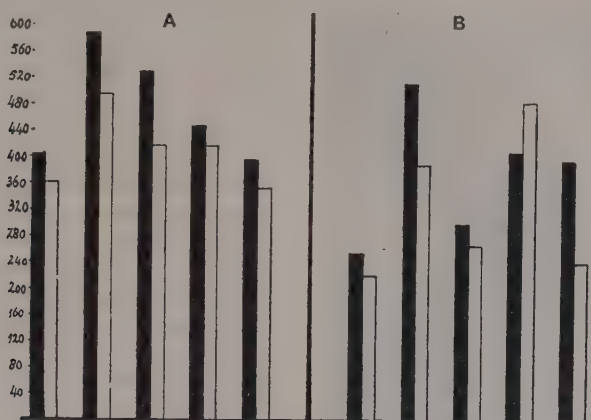


FIG. 204. Diagram showing the Differences in Respiratory Exchange during and after Abolition of decerebrate rigidity of a Cat.

A, oxygen consumption; B, CO_2 output. Black column, during decerebrate rigidity; white column, after abolition of rigidity. (DUSSEY DE BARENNE & BURGER.)

tenth contract, and so on. Such a phenomenon probably would produce a vibration if it did not produce a series of jerks. We should picture rather the muscle fibres going on or coming off duty in a rhythmic manner, rather like a musician producing a stream of music by running his fingers rapidly up and down the keys.

THE IMPORTANCE OF NECK REFLEXES. We must now consider the different nervous mechanisms which modify the postural tone set up by the processes described in previous sections. First in importance come neck and labyrinth kinæsthetic impulses. With regard to the former, suppose that a decerebrate animal be also deprived of its labyrinths. If the head be rotated about the long axis of the trunk so that the chin moves towards the left shoulder, it will be found that the left fore limb extends and that the right fore limb suffers decreased extension. Similar phenomena are sometimes seen pathologically in man (Fig. 205). Experiment shows that it is the turning of the 'atlas' vertebra on the 'axis' which brings about this modification of postural tone. Suppose in another experiment that the neck be bent so that the right ear approaches the right shoulder, it will be found that the extensor tonus in both right front and right hind limbs

is increased, while that in both left front and left hind limbs is diminished. Suppose that in a third experiment the head be raised by applying pressure under the chin, thus bending the neck upwards, then observation will show that the extensor tonus of the front limbs is increased while that of the hind limbs is decreased until no further extension of the front limbs is possible. If the pressure under the chin is continued, the animal will rise on its hind legs, the front legs leaving the ground altogether. This extension of the hind limbs will go on until the animal is fully extended. It will be found on analysing the above effects that in every case the modification in tonus is that which will enable the animal to restore the head to the normal position with respect to the outside world. These modifications in posture disappear on cutting the posterior roots to the neck.

IMPORTANCE OF LABYRINTHINE IMPULSES. It is possible to study the effects of the labyrinths, and at the same time to exclude the neck kinæsthetic impulses which we have just considered, by fixing a plaster of



FIG. 205. Hydrocephalic Infant. Turning of head to left gives increased tonus of left arm. (MAGNUS.)

Paris collar between head and trunk in such a way that relative movement is prevented. It is now possible to move the animal about in different positions and thus ascertain the effects of the labyrinths on the animal as a whole. For example, on placing the animal on its back there is a marked increase in the extensor tonus of both front and hind limbs. The same kind of tonus, but not so marked, is shown on placing the animal on its side, and the tonus disappears entirely if the animal is placed on its belly. These modifications in postural tone disappear if the labyrinths are destroyed.

COMBINED EFFECTS OF LABYRINTH AND NECK REFLEXES. When we investigate animals in which both labyrinth and neck kinæsthetic impulses are allowed to modify postural tone, we find that the

first effect is for the head to right itself under the influence of the labyrinth. This produces some rotation of the head in relationship to the body which, in its turn, causes kinæsthetic neck impulses to be aroused, and these cause such a modification in the tonus in the fore limbs that they right themselves with the disappearance of the bending of the neck; but this will have produced a bending of the trunk between front legs and hind legs, thus setting up kinæsthetic impulses in the trunk. These affect the postural tone of the hind legs in such a way that they also right themselves. The whole of the animal has thus got piecemeal into the normal position.

COMPENSATORY POSE OF THE EYES. By experiments very similar to those described above, it is possible to show that both kinæsthetic sensations from the neck and sensations from the labyrinths contribute to produce deviations of the eyes which are always of a compensatory nature. That is to say, the tendency is always to preserve the same visual field as would obtain if the head and neck were in their normal positions. Suppose, for example, that an animal with labyrinths destroyed has its head turned so that its left ear approaches its left shoulder. Then the eye muscles will

rotate the eyes to the right, that is the eye axes will look in the same direction as they were at first. The retinal image will thus be the same after the head rotation as it was at first, except for the precise points at which the visual fields are curtailed by the images of the bridge of the nose, brow, &c. Similarly, if by applying pressure to the bridge of the nose the neck be bent downward, the eyes will be found to make compensatory rotation in an upward direction, this being accompanied by a corresponding elevation of the upper lid. On the other hand, if an animal with labyrinths retained has its head placed in a plaster of Paris collar and the effects of moving it in different directions be tested, it will be found that the rotations of the eyes are still such as tend to compensate for the movements which have taken place. Under normal circumstances both these sets of impulses operate together.

SUMMARY OF FACTORS CONCERNED WITH POSTURAL REFLEXES. We have considered in previous sections the effects on postural reflexes of vision, vestibular organs, and kinæsthetic sensations from the neck muscles. We must now indicate the importance of skin sensations. Suppose, for example, that an animal has had the labyrinths destroyed, is temporarily blindfolded and also has its neck in a plaster of Paris collar; it will be found that placing the animal lying on its side on a table will still cause it to exhibit normal reflex righting behaviour. That is, first its fore-limbs and then its hind limbs will right themselves so that it can stand in the normal position if it wishes to do so. If, now, flat boards be placed on either side of it and these be lightly clamped together in such a way that pressure is exerted equally on the skin on both sides of its body, then, if it be placed on its side, it makes no attempt whatever to right itself. If the boards be removed and the skin sensations thus restored to normal, it will right itself, or, if the eyes be unbandaged, or if the plaster of Paris collar be removed, it will do so; further, an animal with intact labyrinths will right itself even if it is deprived of the other factors that we have mentioned. These experiments clearly show that each one of these factors alone may bring about the normal righting of the animal. When they collaborate, great precision and promptness in righting results.

CHAPTER XXII

THE AUTONOMIC NERVOUS SYSTEM

In the medulla oblongata it is easy to differentiate the central grey matter connected with the peripheral nerves into two categories, viz. splanchnic and somatic. Each of these two sets of nerves possesses both afferent and efferent fibres. Gaskell has suggested that the same arrangement would hold for any typical segmental nerve, which would therefore have four roots, viz. two somatic—the motor and sensory roots distributed to the skin and skeletal muscles—and two splanchnic roots, also motor and sensory, and composed of small fibres distributed to the viscera or structures which are visceral in origin (*e.g.* developed from the branchial arches). In the medulla the somatic efferent fibres, such as the sixth and twelfth nerves, arise from the column of large cells lying in the floor of the fourth ventricle close to the middle line. The splanchnic fibres, *e.g.* those of the facial and vago-glossopharyngeal nerves, arise from columns of cells—the nucleus ambiguus and the facial nucleus, lying more laterally and deeper, below the surface of the ventricle. The motor root of the fifth would also belong to the same system. In the spinal cord the visceral fibres arise in the cells of the lateral horn, *i.e.* from a situation corresponding to the splanchnic motor nuclei of the pons and medulla. Whereas, however, the splanchnic afferent nerves, such as the glossopharyngeal, and perhaps the sensory nucleus of the fifth, form a well-marked splanchnic system of nuclei in the medulla, in the cord the afferent fibres from the viscera pass in with the afferent somatic fibres, and their immediate connections in the cord are as yet unknown.

The autonomic system of nerves include the sympathetic system (properly so called) and some of the cranial and sacral nerves. The sympathetic system (Fig. 206) is composed of a chain of ganglia lying on each side of the vertebral column, there being as a rule one ganglion to each spinal nerve root. But in the cervical region these ganglia are condensed into two, the superior and inferior cervical ganglia, united by the cervical sympathetic trunk; and the upper three or four thoracic ganglia on each side are condensed to form the 'stellate' ganglion. At the bottom of the chain there is only one coccygeal ganglion for the coccygeal vertebræ.

In the abdomen is a second system of ganglia, in special connection with the abdominal viscera, lying in front of the aorta and surrounding the origins of the large arteries to the alimentary canal. These are the semi-lunar, or solar, ganglion and the superior mesenteric and inferior mesenteric ganglia.

In the organs themselves we often find a third system of ganglion cells, either scattered or collected to form small ganglia. These isolated ganglion cells as a rule have no connection with the fibres of the sympathetic system, but, as we shall see later, lie on the course of the impulses descending by other nerves of the autonomic system, the so-called parasympathetics, *e.g.* the vagus or the pelvic visceral nerves. The three systems of ganglia have been distinguished as the *lateral*, *collateral*, and *terminal* ganglia.

The (lateral) ganglia of the sympathetic chain are connected with all the

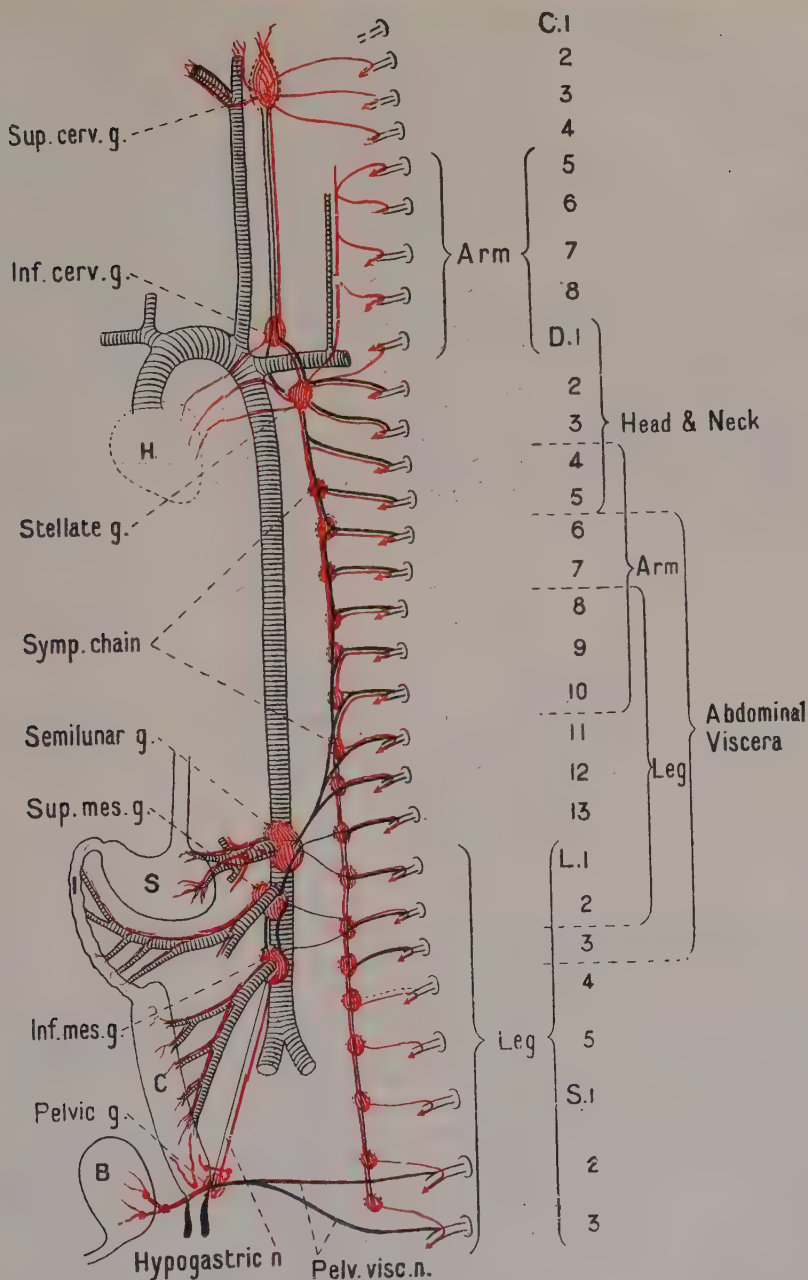


FIG. 206. Diagrammatic Representation of the Distribution of the Sympathetic System.

The black lines represent the medullated pre-ganglionic fibres, such as those making up the white rami communicantes, while the post-ganglionic fibres are printed in red. On the extreme right of the figure is indicated the general distribution of the white rami arising from the several nerve roots, while the double brackets point to the nerve roots making up the limb plexuses.

- H. Heart.
S. Stomach.
I. Small intestine.

- C. Colon.
B. Bladder.

spinal nerves, just after they have given off their posterior divisions, by means of the *rami communicantes*. These *rami communicantes* are of two kinds : white rami consisting of small medullated fibres, and grey rami composed almost exclusively of non-medullated nerves. It has been shown by Gaskell that the white rami are formed by fibres which have their origin in the spinal cord and perhaps also in the posterior root ganglia ; whereas the grey rami represent fibres which, arising in the sympathetic ganglia, run back to join the spinal nerves (Fig. 207). The visceral outflow represented by the white rami is limited to a distinct region of the cord, viz. from the first thoracic to the third or fourth lumbar nerve roots ; whereas the grey rami pass from the sympathetic to all the spinal nerve roots. It is found by experiment that stimulation of a limited number of white rami produces all the effects that can be evoked by stimulation of the grey rami, showing that the impulses leaving the cord pass upwards and downwards in the sympathetic system and are broken somewhere in their course, being transferred to a fresh relay which, by means of non-medullated nerves, carries them on to their destination.

Finally, in certain organs of the body are to be found plexuses of nerve structures, including both ganglion cells and fibres, which must be regarded

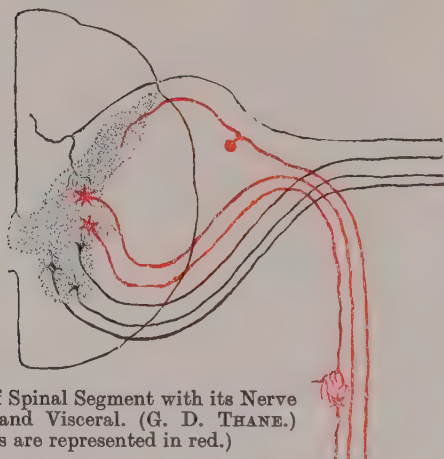


FIG. 207. Diagram of Spinal Segment with its Nerve Roots, Somatic and Visceral. (G. D. THANE.)
(The visceral roots are represented in red.)

as local nerve centres, capable of carrying out co-ordinated acts in response to stimuli, independently of the central nervous system. It seems probable that these systems are to be regarded as analogous rather to the diffuse neuro-fibrillar system of an animal, such as the medusa, than to the synaptic nervous structures characteristic of the central nervous system of vertebrates. In the latter, the direction and effect of any impulses are determined by the synapses intervening between various systems of neurones and allowing the passage of the impulse only in one direction. This law of forward direction has not been proved to hold good for the primitive nerve-net systems : an impulse apparently spreads equally well in either direction. As a type of this peripheral diffuse nerve system may be cited Auerbach's and Meissner's plexuses in the wall of the alimentary canal. How far we are to regard the nerve nets in other viscera, such as the heart and the bladder, as conforming to this type is still a moot point, and will be discussed in dealing with the origin of the heart beat.

The relationships of the white and grey rami are strikingly illustrated in the case of the pilomotor systems of nerves. These, in the cat, arise from the cord by the anterior roots from the fourth thoracic to the third lumbar

inclusive. Passing by the white rami to the sympathetic system, they travel upwards and downwards and end by arborisations in the various ganglia of the main chain. From the cells of each ganglion a fresh relay of fibres starts, which runs as a bundle of non-medullated nerves (the grey ramus) to the corresponding spinal nerve, with which it is distributed to its peripheral destination. Each grey ramus causes erection of the hairs above one vertebra, whereas stimulation of one white ramus causes erection over three or four vertebrae, showing a distribution of the fibres of the white ramus to the cells in several successive ganglia.

These pilomotor fibres in the cat have the following distribution :

(1) For the head and upper part of the neck the fibres arise by the fourth to the seventh thoracic anterior roots, and have their cell stations in the superior cervical ganglion. They travel as small medullated nerve fibres

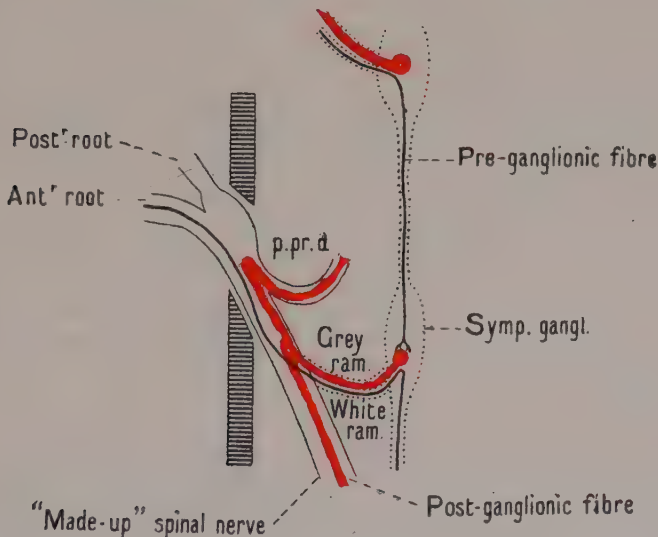


FIG. 208. Diagram to show the manner in which a Spinal Nerve is completed by the entry of a Grey Ramus, containing Fibres derived from Cells in the Sympathetic Chain. (After LANGLEY.)

p.pr.d. Posterior primary division. (The post-ganglionic fibres are represented in red.)

from the white rami up the sympathetic chain, through the stellate ganglion and ansa Vieussensii and up the cervical sympathetic.

(2) The next set of nerve fibres have their cell station in the stellate ganglion. The white rami arise from the fifth to the eighth thoracic nerves, while the grey rami pass to the nerve roots from the third cervical nerve to the fourth thoracic nerve.

(3) The remaining nerves, supplying all the rest of the body and tail, arise by the white rami from the seventh thoracic to the third or fourth lumbar nerve, and are distributed as grey rami to all the spinal nerves below the fourth thoracic.

We thus see that, in speaking of the functions of a spinal nerve root, we must clearly distinguish whether we mean the root as it arises from the spinal cord, in which case its visceral functions will include those of its white ramus, or whether we mean the made-up or complete spinal nerve after it has received its grey ramus (Fig. 208). In the latter case the visceral functions of the root will be more restricted than in the former case, and will have a

different distribution. In stimulating the nerve roots inside the spinal canal it is sometimes possible, by weak stimuli, to display the functions of the corresponding white ramus, and then by increasing the stimulus to get superadded the effects due to the excitation of the grey ramus in the made-up nerve, in consequence of the spread of current.

"When, for example, the eleventh thoracic anterior roots are stimulated in the spinal canal with weak shocks, a fairly long strip of hairs in the lumbar region will be erected, the maximum movement of the hairs being near the middle of the strip. This marks the area of distribution of the pilomotor nerves given by the eleventh thoracic nerve to the sympathetic. If then the strength of the shock be increased to a certain point, the hairs in the long strip will of course be erected as before, but in addition there will be energetic erection of hairs in a short strip a little distance above the long strip, and separated from it by a quiescent region. This short strip is the same as that affected by stimulating the grey ramus or the dorsal cutaneous branch of the eleventh thoracic nerve. It marks the area of distribution of the pilomotor fibres received by the spinal nerve from the sympathetic." (LANGLEY.)

We may now indicate briefly the main course and functions of the fibres of the sympathetic system.

(1) The head and neck are supplied by fibres leaving the spinal cord by the first five dorsal nerves (chiefly by the second and third). They all have their cell stations in the superior cervical ganglion. They convey :

Vaso-constrictor impulses to the blood vessels.

Dilator fibres to the pupil.

Secretory fibres to the salivary glands and sweat glands.

Vaso-dilator fibres to the lower lip and pharynx (?).

(2) The *thoracic viscera* (heart and lungs) are supplied by the same five nerve roots. The cell stations of these fibres are however situated in the stellate ganglion. They convey :

Accelerator or augmentor impulses to the heart.

Vaso-dilators to coronary vessels.

Broncho-dilators to bronchioles.

(3) The *abdominal viscera* receive fibres from the lower six dorsal nerves and the upper three or four lumbar. Most of these fibres run through the sympathetic chain without making any connection with the ganglia, and have their cell stations in the collateral ganglia of the solar plexus, the semi-lunar and superior mesenteric ganglia. On their way to these ganglia they form the greater and lesser splanchnic nerves. Their functions are :

Vaso-constrictor for stomach and small intestine, kidney and spleen.

Probably vaso-dilator for the same viscera.

Inhibitory for both muscular coats of stomach and small intestine.

Motor for ileocolic sphincter.

Secretory to the suprarenal medulla.

Vascular and glycogenolytic to the liver.

(4) The *pelvic viscera* are supplied by the lower dorsal and upper three or four lumbar nerve roots. These fibres also pass by the main chain to make connections with the cells, chiefly in the inferior mesenteric ganglia. They convey :

Vaso-constrictor impulses to pelvic viscera.

Inhibitory fibres to colon (both coats).

Motor and also inhibitory fibres to bladder.

Motor fibres to retractor penis.

Motor and inhibitory fibres to uterus and vagina.

(5) The fore limb receives nerves from the white rami of the fourth

to the tenth thoracic nerves. All these fibres are connected with cells in the stellate ganglion. They convey :

Vaso-constrictor impulses to the blood vessels.

Secretory nerves to the sweat glands.

(6) The hind limb is supplied by the nerve roots from the eleventh thoracic to the third lumbar inclusive. The cell stations of these fibres are situated in the sixth and seventh lumbar and first sacral ganglia. They convey :

Vaso-constrictor impulses.

Secretory nerves to the sweat glands.

Every fibre of the sympathetic system is thus in some point of its course interrupted by a nerve cell, and Langley has shown that this is the only cell-break in the fibre. This applies not only to the sympathetic fibres but also to the fibres of the other visceral nerves. Each fibre therefore can be regarded as made up of two sections—a *pre-ganglionic* fibre arising in the central nervous system and passing down to a ganglion as a fine medullated nerve fibre, and a *post-ganglionic* fibre arising in this ganglion and continued generally as a non-medullated fibre to its peripheral distribution.

This transference from one system to another involves the passage across a synapse and a nerve cell. The situation of this synapse may be easily revealed by utilising the action of nicotine, first studied by Langley. If nicotine be applied to a sympathetic ganglion, it first stimulates and then paralyses any junction between axon termination and nerve cell which may lie in the ganglion. Intravenous injection of nicotine therefore causes a primary general excitation of all visceral ganglion cells. There is an enormous rise of blood pressure, which may be accompanied by other sympathetic effects, such as dilatation of the pupil, secretion of saliva, erection of the hairs, and so on. This rise rapidly passes off, and it is then found impossible to evoke any reflex visceral effects or any contraction, *e.g.* of the blood vessels by stimulation of the spinal cord ; the passage of the impulses is blocked in every one of the visceral ganglia. By observing the effects of stimulation of a nerve before it enters a ganglion and then painting the ganglion with nicotine, and again trying the effects of excitation, it is easy to determine whether the nerve fibres which were excited in the first case form any connections with the nerve cells of the ganglion. In the strength in which it is usually applied by doctors and dentists nicotine is without effect on nerve fibres.

THE CRANIAL AUTONOMIC FIBRES

Visceral fibres are contained in the following cranial nerves—the third, seventh, ninth, tenth and eleventh.

Third Nerve. The visceral fibres of this nerve pass to the ciliary ganglion in the orbit where they end ; the post-ganglionic fibres from this ganglion form the short ciliary nerves which innervate the sphincter pupillæ and the ciliary muscles.

Seventh Nerve. The autonomic fibres of the facial arise from the medulla in the intermediate nerve of Wrisberg, which is practically the anterior continuation of the ninth, tenth and eleventh nerves. From the seventh nerve is derived the chorda tympani nerve, which supplies vaso-dilator nerves to the tongue, the submaxillary and sublingual glands, and secretory fibres to these glands and to the naso-pharynx.

The cell stations of these nerves lie peripherally. Those of the sublingual gland in the so-called submaxillary ganglion ; those of the submaxillary gland in the hilum of this organ. It is probable that the seventh sends also

pre-ganglionic visceral fibres to the sphenopalatine ganglion, whence a fresh relay of fibres—post-ganglionic—runs with the branches of the fifth nerve, to supply secretory fibres and possibly vaso-dilator fibres to the mucous membrane of the nose, soft palate and upper part of the pharynx. The glossopharyngeal or *ninth nerve* sends fibres, which evoke secretion as well as vaso-dilatation in the parotid gland, *via* the otic ganglion. Probably also dilator fibres leave this nerve to supply vessels at the back of the tongue.

The Vagus. The efferent visceral fibres of the tenth and eleventh nerves arise in the same column of cells as the two nerves just considered. Most of the fibres run in the vagus. They include motor fibres to the oesophagus, stomach and small intestines as far as the ileocolic sphincter; inhibitory fibres to the heart; motor fibres to the unstriated muscles of the bronchi; and secretory fibres to the gastric glands. The cell stations of these fibres are apparently situated peripherally, the jugular ganglion and the ganglion of the trunk of the vagus being in all likelihood responsible only for the afferent fibres in this nerve. Nicotine, therefore, abolishes any effect of stimulating the vagus in the neck, though inhibition of the heart can still be produced on excitation of the post-ganglionic fibres arising from the cells in the sinus venosus.

SACRAL AUTONOMIC FIBRES

These all run in the pelvic visceral nerve, also called *nervus erigens*. This nerve is connected with a collection of ganglia lying in the hypogastric plexus at the base of the bladder. It has the following functions:

Dilator to vessels of the penis (hence its name of *nervus erigens*).

Motor to bladder, colon, and rectum.

Inhibitory to sphincter muscle of bladder.

Inhibitory to retractor penis.

It will be observed that in many cases the viscera get their nerve supply from both sets of visceral nerves, and that in such cases the two sets of nerves are antagonistic in function. It is impossible, however, to draw a sharp line between the functions of the two sets, since the same nerve may be motor for one set of muscular fibres and inhibitory for another set in the same viscus. Thus the colonic branches of the inferior mesenteric ganglion are motor (constrictor) for the blood vessels and inhibitory for the muscular walls of the colon. While the sympathetic nerve supply is inhibitory for nearly the whole intestinal musculature, it produces strong contraction of the band of muscle forming the ileocolic sphincter. In the bladder there is no doubt that the sympathetic supply includes both inhibitory and motor fibres, the predominating effect on excitation of the nerve varying from one species of animal to another.

FUNCTIONS OF THE SYMPATHETIC AND PERIPHERAL GANGLIA

These ganglia consist of a mass of nerve cells embedded in connective tissue, each cell being surrounded by a special capsule of endothelial cells. The nerve cells, though in section resembling those in a posterior root ganglion, differ from these in being multipolar, each cell probably possessing one axon and several dendrites. The dendrites end in little arborisations round adjacent cells.

Since the main nervous system is characterised by the possession of nerve cells, it was formerly thought that any collections of nerve cells must

partake of the co-ordinating and reflex functions of the central nervous system, *i.e.* must act as local nervous centres. All efforts have failed, however, to prove the existence of such a function, and we must conclude that the sole use of these ganglia is to serve as distributing centres. We may assume that one pre-ganglionic fibre divides, and the branches arborise round several cells (Fig. 209), whence new fibres arise to carry the impulse to the periphery—an impulse in the case of which there is no need for any minute localisation. Indeed the essential part of a nerve centre is not the nerve cells at all, but the presence of a complex tangle of fibres, rendering possible the passage of impulses in all directions, the passage of an individual impulse being limited by reason of the varying 'strength' of the impulse and the varying resistance of the many possible tracts. In many invertebrata the nervous

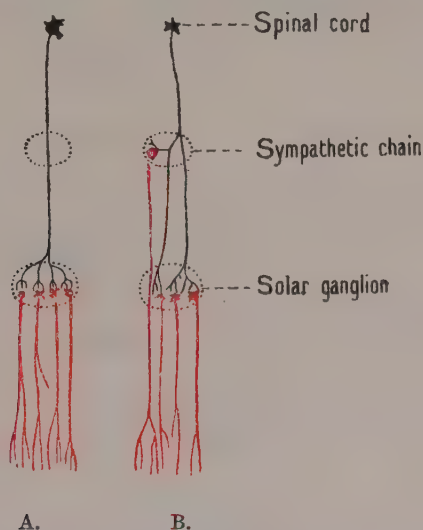


FIG. 209. Figure to show the probable Mode of Connection of the Fibres of the Splanchnic Nerve with Nerve Cells. (After LANGLEY.)

- A. Usual type, all the fibres passing through the lateral chain to end in the collateral ganglia of the solar plexus. B. Alternative condition, in which a small minority of the fibres have their cell stations in the sympathetic chain.

The pre-ganglionic fibres are black, the post-ganglionic red.

system consists of a punctated material composed of a dense interlacement of fibrils, while the cells lie outside the centres and have one thick process dipping into the nervous mass, from which process both axon and dendrites arise. In this case, as we have seen, extirpation of the cell bodies does not destroy the capacity of the remaining fibrillar substance to act as a reflex centre. Such a complex of fibres is found in mammals in the plexuses of Auerbach and Meissner, which act as local nerve centres for the intestine. But all such mechanism is wanting in the sympathetic ganglia, which contain neither association fibres between different cells of a ganglion nor commissural fibres between the cells of adjacent ganglia. All the fibres in a sympathetic ganglion have either entered it from the white rami or are destined to leave it as fibres of grey rami.

Several responses in peripheral ganglia, formerly described as reflexes, as, *e.g.*, in the 'submaxillary' ganglion, have been proved not to be such. There is, however, a certain group of phenomena which can be elicited in

sympathetic ganglia, and which have been termed by Langley and Anderson *axon reflexes*. If, for instance, we divide all the nerves going from the sympathetic chain to the inferior mesenteric ganglion, leaving the bladder connected with this by the hypogastric nerves, and then after dividing the left nerve stimulate its central end, we obtain a contraction of the right half of the bladder. This effect is abolished by painting the inferior mesenteric ganglion with nicotine, showing that the activity of the cells of this ganglion is involved in the process. It has been shown, however, by Langley and Anderson that this is not a true reflex, but is rather analogous to Kühne's gracilis experiment (*cf.* page 203). A pre-ganglionic fibre arriving at the inferior mesenteric ganglion branches, one branch ending round the cells of the ganglion, while the other branch passes down in one hypogastric nerve to a cell situated near the base of the bladder (Fig. 210). When, therefore, we stimulate this nerve, we are stimulat-

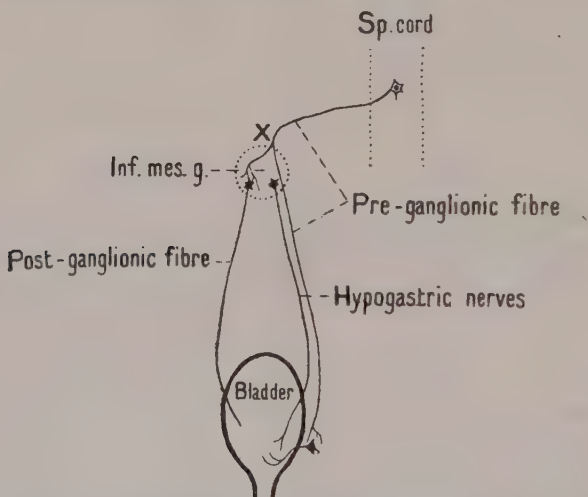


FIG. 210. Diagram to illustrate Langley and Anderson's explanation of the Hypogastric Reflex as an Axon Reflex.

The division of the axon where the propagation or 'reflexion' takes place is at X.

ing a pre-ganglionic fibre, and the excitation spreads up to the point of junction of the two branches and then down the other branch to excite the cell in the inferior mesenteric ganglion. We thus obtain an apparent motor reflex by stimulation of a nerve which is itself motor. Similar pseudo-reflexes can be obtained along the abdominal chain on the pilomotor nerves, but furnish no grounds for ascribing the property of reflex centres to peripheral ganglia. On the other hand, these axon reflexes are very similar to the spread of the excitatory process which occurs in the diffuse nerve network of an animal such as the medusa. Irreciprocity of conduction would seem therefore to be the most useful criterion of a true reflex.

INHIBITION IN PERIPHERAL GANGLIA. The existence of ganglion cells in the course of the nerves to visceral muscles has often been supposed to account for certain peculiarities in the innervation of visceral, as compared with skeletal, muscle. Chief among the differences between these two kinds of muscles is the frequency with which inhibition may be brought about in visceral muscle by stimulation of peripheral efferent nerves. In skeletal muscle, inhibition is known only as the result of alteration of the activity of the motor centres from which it is supplied. It has therefore been thought that the peripheral ganglia of visceral muscle play the part of the motor spinal centres

of skeletal muscle, and that when we excite an inhibitory nerve, say to the intestine, we are interfering with and diminishing a tonic state of activity which has its seat in a peripheral ganglion cell connected with the visceral muscle.

This view, which was first put forward by Claude Bernard, has been specially defended by Dastre and Morat. These observers point out that vasodilator action diminishes or disappears as nerve strands are stimulated more and more peripherally, and conclude that the vasodilator fibres run to the sympathetic ganglion and inhibit their tonic action. The untenability of this view has been demonstrated by Langley. Thus the chorda tympani fibres run to a local nerve centre in the hilum of the submaxillary gland. On Bernard's theory stimulation of the fibres peripherally to the centre should cause contraction of the arteries; but it is found that, after paralysis of the ganglion by nicotine, stimulation of the post-ganglionic fibres causes dilatation, so that the nerve fibres given off from the local centre are not vasoconstrictor but vasodilator. Moreover it can be shown that the sympathetic fibres which do cause constriction make no connection with the cells in the hilum of the gland, but run on the walls of the arteries to their distribution. These fibres are connected, not with cells of the submaxillary ganglion (the local nerve centre), but with cells in the superior cervical ganglion.

We must conclude that the inhibitory nerves in these visceral structures exert their influence directly on the peripheral tissue, and not by a diminution of activity of a tonically acting peripheral "centre."

AFFERENT FIBRES OF THE AUTONOMIC SYSTEM

The supply of afferent fibres to the viscera is very small in proportion to the supply to the outer surfaces of the body. According to Langley, in a visceral nerve such as the hypogastric, only about one-tenth of the medullated fibres are afferent, and the proportion of afferent fibres in the splanchnic nerves is probably not very different from this. At the two ends of the alimentary canal, *i.e.* at the mouth and anus, the afferent visceral fibres become of more importance, since through their means co-operative somatic reflexes have to be excited as well as the simple visceral reflexes. Thus in the pelvic visceral nerve about one-third of the fibres are afferent, and the vagi contain a large number of afferent fibres from the lungs as well as from the other viscera innervated by it.

According to Dogiel, afferent visceral fibres arise from sensory cells of the sympathetic ganglia and, passing in to the posterior spinal ganglia, divide and form pericellular endings round a special type of posterior root cell, the axon from which divides again into a number of branches ending in connection with typical unipolar cells. Thus, according to this observer, a few afferent sympathetic fibres can stimulate a considerable number of posterior root cells. Langley, however, has not been able to obtain any experimental confirmation of the origin of branching afferent fibres from cells of the sympathetic system.

It is probable that the afferent fibres of the visceral nerves arise, like those of the somatic system, from ganglion cells of the posterior spinal ganglia. Every white ramus contains afferent fibres, stimulation of which may evoke a rise of blood pressure as well as movements of the skeletal muscles. In spite of the supply of afferent fibres to the viscera, most of these organs are very insensitive to ordinary stimulation such as handling or cutting. In operations on man for resection of the gut, if the abdominal cavity be opened under local or general anæsthesia, subsequent cutting and suturing of the gut may be conducted without any anæsthetic and without causing any pain to the patient. On the other hand, impulses may arise in the afferent nerve endings of the viscera, as a result of disease, or of certain forms of stimulation, *e.g.* stretching or compression, which may reach consciousness and give rise to the sensation of pain. This pain is not localised in the viscera, but is referred to certain parts of the surface of the body. When the afferent autonomic fibres of a nerve are the seat of pain, the primary referred pain is in the area of the cutaneous somatic fibres

of the nerve. It has been shown by Mackenzie and by Head that visceral disease may cause hyper-sensitivity of the corresponding areas of the skin, and a method has been elaborated by these observers for utilising this referred pain or skin tenderness as a means of localising the site of the disease.

THE SYMPATHETIC INNERVATION OF VOLUNTARY MUSCLE

Histological examination of skeletal muscle shows the presence of non-medullated fibres, ending in the muscle fibres, either on or under the sarcolemma, sometimes forming simple end plates. There is much divergence of opinion both as to the origin and destination of these fibres, and as to their significance. Many of them are undoubtedly sympathetic in origin. According to Hunter the sympathetic supply to voluntary muscle is concerned with the maintenance of 'plastic tone.' The exaggerated plastic tone or rigidity, which occurs in man as a result of lesions of the motor cortex or the pyramidal tracts, is said to have been considerably lessened and the patient's condition improved, by section of the sympathetic supply to the limb. Application of adrenaline as well as stimulation of the sympathetic nerve in the frog have been said to quicken the process of recovery from fatigue. Various observers have failed, however, to obtain any effects of the sympathetic system on skeletal muscle, so that we must await further experimental information before making any definite statement in the matter.

THE SENSE ORGANS

CHAPTER XXIII

VISION

1.—PHYSICAL PROPERTIES OF LIGHT

LIGHT is a form of energy, and consists of electro-magnetic waves which travel with a velocity of 184,000 miles per second through the ether. Since we receive light from the stars, we conclude that the ether permeates the whole of space. We know also from electrical experiments that the ether also permeates matter. We might expect therefore that light would freely pass through matter, or in other words that all matter would be transparent. This is not the case, however, because most forms of matter have the property of absorbing light energy; and therefore the property of transparency is relatively rare.

LIGHT IS A FORM OF WAVE MOTION. Because of this, one of its characteristic properties is amplitude. But since this depends on the amount of light energy present, it is equivalent to what is known as intensity. The other characteristic property of wave motion is wavelength. In the case of ordinary light it is found by experiment that a whole gamut of waves varying greatly in length is present. Those falling between certain limits are able to stimulate the eye, and are therefore called visual rays. These limits are slightly less than 8000 Ångström units* for the longer limit and 4000 A.U. for the shorter. Rays whose wavelength falls outside these limits are invisible to the eye, and are called infra-red rays when they are too long, and ultra-violet when they are too short. Of longer wavelength than the infra-red rays are the wireless waves, while of shorter wavelength than the ultra-violet rays are the X-rays. Since the infra-red rays are able to stimulate the sensory end organs of the skin which respond to heat, they are also called heat rays; while the ultra-violet rays, from their ability to promote certain chemical reactions, and notably those used in photography, are called actinic rays. There is, however, no such sharp line of demarcation between the three groups as the use of these terms might be thought to imply.

THE SPECTRUM. It is possible by suitable apparatus to cause the constituent rays in a beam of light to arrange themselves according to their wavelength. When thus arranged they are said to form a spectrum. The apparatus is therefore called a spectroscope. The visible rays thus arranged are seen as a coloured band which has the following appearance. Visibility usually begins at about 8000-7800 A.U., the rays of longest wavelength being red. As the wavelength becomes shorter the colour gradually changes to orange, the transition being at about 6500 A.U. From orange the colour changes to yellow, at about 6000 A.U.; from yellow to green at 5500 A.U., to blue-green at 5000 A.U., to blue at 4500 A.U., and to violet at 4000 A.U. The violet extends to 3800 A.U., where visibility ceases. The spectrum exhibits therefore a gradual change of colour with wavelength. Above the red is the invisible region occupied by the infra-red or heat rays, and below the violet the invisible ultra-violet or actinic rays, as explained above.

The colours of the spectrum have important properties which form the foundation of the science of colour mixture. If the spectrum produced from white light is caused to fold up again, it is found that white light is re-formed. But white light is produced if certain pairs of colours only are caused to combine in the correct proportion. Thus red (6562 A.U.) and blue-green (4921 A.U.) when mixed correctly form white light, so also do yellow (5636 A.U.) and violet (4330 A.U.). Such pairs are called *complementary colours*. But since there is in the spectrum a gradual transition from one colour to the next, so there are between red and yellow an infinite number of rays of different wavelength, each of which has its complementary colour, between blue-

* An Ångström unit = one ten-millionth of a millimetre, or $0.1 \mu\mu$.

green and violet. If, therefore, from white light we remove one of a pair of complementary colours, the other member of the pair will be left unneutralised, and the light thus becomes tinted with its colour. Green rays do not possess a complementary in the spectrum; but it is found by experiment that, by combining red and violet to form purple, the required colour may be produced. If we include purple with the spectral colours, we can imagine these colours to form a closed ring. Each colour will then have its complementary opposite to it.

THE SPECTRAL COLOURS have another important property, for if red and yellow are caused to combine, they are found to produce orange, the intermediate colour. If red and green are mixed, then again the intermediate colour, yellow, may be produced. It is found that by varying the intensities of the two components, it is possible to produce orange or yellow-green, or in fact any other intermediate colour at will. Careful experiment shows that the intermediate colour thus formed is no mere approximation but an exact match. If red and green are thus able to combine to form the intermediate colour, while red and blue-green are complementaries producing white by their mixture, the question arises as to the effect produced by mixing red with a colour intermediate between green and blue-green. Experiment shows that a range of colours is produced containing an amount of white light, which varies with the intensities and wavelengths of the combining colours. Colours diluted with white light are spoken of as *unsaturated*.

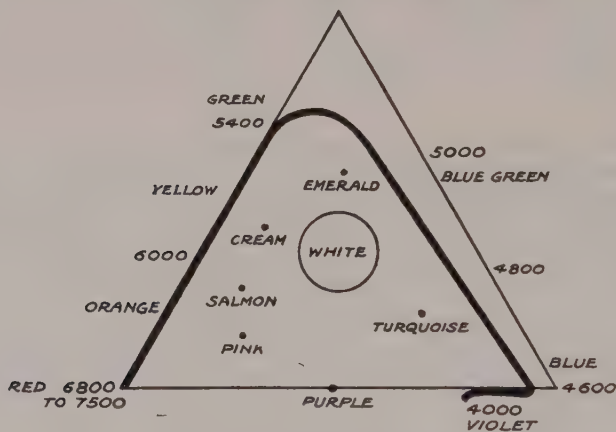


FIG. 211. Colour Triangle.

The black line shows the shape of the curve along which the different rays of the spectrum fall for white to occupy the central position.

In order that the colours produced by a mixture of red and green rays shall be fully saturated, and thus be able to match the colours of the spectrum exactly, the green must not be shorter in wavelength than 5400 A.U. Similar phenomena are to be found at the other end of the spectrum; green and violet, when mixed in various proportions, form colours which match the intermediate spectral colours. With red, green and violet it is therefore possible to match the whole spectrum. But since red and violet, when mixed, form the intermediate purples, it is possible with the three coloured rays to imitate the whole range of colours. Now the purple formed from red and violet is, as we have seen, the complementary colour to green; by means of these three colours it is thus possible to produce white light. It should therefore be possible to match an unsaturated colour as easily as a saturated one. Experiment shows that such is the case. The third property, beside colour and saturation, is *intensity* which depends on the amplitude of the waves. The intensity of the mixture formed by red, green and violet, can therefore be readily adjusted by varying the intensity of each of the three component rays. We may summarise the above facts by stating that, by varying the intensities of the red, green and violet rays, it is possible to match every shade and colour. This statement has been put to the test by Maxwell, Abney and other observers, and has been found to hold good in all cases but one, spectral blue being slightly more saturated than the mixture of green and violet. In describing the complementary pairs of colours, we have mentioned that if the spectral colours are placed in a closed ring, complementary pairs are found to be opposite to one another. If now the three fundamental colours are placed at equal intervals round the ring, we may regard white

as occupying the centre, because it is equidistant from the three fundamentals, and at the same time lies on the diameter between the various colours and their complementaries. If the other spectral colours are arranged in position relatively to the three fundamentals, they form a figure that in shape resembles a triangle more closely than it does a ring. This is due to the facts already mentioned (1) with regard to the exact matching of the spectral colours between red and green, by mixtures of those two fundamental colours; (2) with regard to the approximate matching of the region between green and violet by the mixtures of those colours, and (3) with regard to the exact matching of mauves and purples by mixtures of red and violet. The colour triangle which is shown in Fig. 211 therefore has a purely experimental basis, and has no association whatever with theories of vision.

THE OPTICAL PROPERTIES OF MATTER. All matter absorbs light to a greater or less extent; even substances that are called transparent, like glass and water, absorb strongly when in sufficient thickness. When a body presents a smooth surface to the light rays, some of these are thrown off again as a compact bundle, and the surface is therefore said to reflect light. If, on the other hand, the surface presented to the light rays is rough, the light bundle is split up into a number of separate units which scatter diffusely in every direction. Such a surface is therefore said to diffuse or scatter light. If light is incident on matter, there are thus four different processes that may occur, viz. the light may be partially absorbed, or partially transmitted, it may be partially reflected and lastly it may be partially scattered. In the great majority of cases, all these processes take place to a certain extent, and are found to affect the different parts of the spectrum differently. For example, while the colours of short wavelength are absorbed, those of long wavelength may be almost completely reflected. (A polished copper surface is found to have these properties.) Another example would be a substance which, while absorbing colours of long wavelength, scatters almost completely all colours which belong to the other end of the spectrum. (Basic acetate of copper, *i.e.* verdigris, has this property.) Lastly the case of a fluid may be given which absorbs colours in the middle of the spectrum, while it transmits freely those at the ends. The light transmitted is, therefore, violet in colour (as the appearance of a solution of potassium permanganate or methyl violet shows). Colour is thus due in every case to some difference in the behaviour of the substance towards the various rays of the spectrum. In order to complete the description of colour formation, two other methods should be described by which colour may be produced, namely *fluorescence* and *phosphorescence*. The former term is applied when a substance absorbs light of one colour, and at the same time emits light of another. The latter is applied when a substance emits light for an appreciable time after light has ceased to fall on it.

LIGHT SOURCES fall into two classes, those which emit radiant energy because of the high temperature to which they have been raised, and those which are 'excited' in other ways. The light from the former class as a rule consists of rays of all wavelengths, from the longest heat rays to the shortest ultra-violet. The light from the latter class, on the other hand, is frequently found to consist of rays corresponding to characteristic regions of the spectrum. The mercury vapour lamp may be mentioned as an example of the latter type of light source, which has come into general use. If the visible spectra obtained from a few light sources of the first type are carefully measured, it is found that although rays of all wavelengths are present, there are considerable variations in the intensities of the different rays. This causes variation not only in the colour of the light as a whole, but also affects the colour of objects and the ease with which the eye can judge colours. This variation in the distribution of intensity in the spectrum is found to be accompanied by corresponding changes in the infra-red and ultra-violet. For equal visual intensity, as the temperature of the source is increased, the greater is the amount of ultra-violet light and the less is the infra-red. Moreover as the temperature is raised, the whiter, and therefore the more like daylight, does the light become. Measurements of the energy present in different parts of the spectrum show that much the greater part of the energy is present in the infra-red. These heat rays play no useful part in vision, and may in fact do harm; the greater part of the energy is thus wasted, and for this reason the efficiency of this class of light source is very low. Since raising the temperature of the light source causes the light to approximate more closely to daylight and at the same time reduces the relative amount of the infra-red rays, it effects considerable advantage because it increases efficiency.

THE ENERGY IN THE SPECTRUM is present in greatest amount at the red end, and least at the violet. In spite of this the part of the spectrum with the greatest luminosity to the eye is the yellow. The values obtained by Abney are shown in Fig. 212.

DIFFRACTION AND REFRACTION. Beside the properties of light that have been already considered, namely the relationship between actinic, visual and heat rays,

and the effects of colour mixture, there are others of importance to vision: (1) The property of travelling in straight lines; (2) of suffering refraction; (3) of causing chemical change. The first property can be easily demonstrated by investigating shadow formation. But it should be noted that straight line propagation is only approximate, for it can be shown that at the edge of a light ray there may be considerable deviation. This effect is called diffraction, and will be considered in greater detail later. The second property, namely that of suffering refraction, is found to take place whenever light travels from a medium of one optical density (refractive index) into that of another. Briefly, refraction consists of a deviation of the light rays towards the normal to the surface when entering a denser medium, and away from the normal on entering a lighter. Rays of long wavelength tend to keep their original direction more than those of short wavelength. Red rays are therefore less refracted than orange rays, and orange less than yellow, and so on according to wavelength. It is in this way that the spectrum is formed in the special apparatus for experiments on colour mixture referred to above.

But the most important effect of refraction, from the point of view of vision, is the formation of an image by a lens. This action may be briefly explained by considering what will happen to a beam of light when it encounters a mass of high optical density having a convex spherical surface. Since the rays on entering are deviated towards the normal to the surface, it is clear that rays that have entered near the edge of the lens will be bent towards one another, and will therefore approach as they travel through the lens substance, till they ultimately meet at the focus with all the other rays that have entered the lens from the same source as themselves. But if there be a number of different sources, then the rays from each are found to form

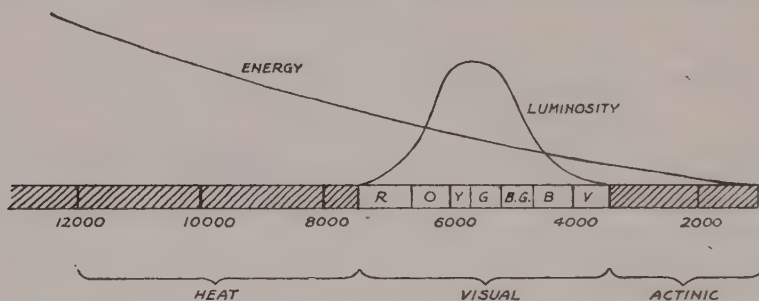


FIG. 212. Curves showing Relative Energy and Luminosity of different Regions of the Spectrum.

their own focus, at a position that may be determined either by experiment or by the rules of geometry. The positions of the different foci are found to bear the same relationship to one another as those of the original sources, or in other words an image is produced.

PHOTO-CHEMICAL CHANGE, which is the third property of light mentioned above, is well illustrated by photography. The most important principle of light action is that light, to cause chemical change, must be absorbed (Draper's law). For example, an ordinary photographic plate which is found to be opaque to blue, violet and ultra-violet rays, and to be transparent to the rest of the visible spectrum, is therefore sensitive to the former rays but inactive to the latter. Further by colouring the plate by a dye which absorbs red, yellow and green, it is possible to make the plate react to these rays. Draper's law is therefore obeyed. Chemical reactions caused by light are of many types, but may be divided into reversible and irreversible. The former type of reaction occurs only so long as the light acts (the change from CO to oxyhæmoglobin may be given as an example), while the latter type remains in the final state that has been reached (the changes in a photographic plate may be given as an example). There is further another and more complicated type which, when once started by an incident beam of light, goes on automatically with an evolution of energy until the reaction is completed. These effects of light are probably of great importance in connection with vision and will therefore receive further consideration later.

2.—EYE MOVEMENTS

ANATOMY OF THE ORBIT. The eyeball and its accessory structures lie in the bony orbital cavity, surrounded and padded by a mass of semi-liquid fat. The cavity

is pierced by several apertures, through which pass various vessels and nerves. The optic nerve enters through an aperture of its own, the optic foramen, together with the ophthalmic artery. Most of the other vessels and nerves concerned with vision pass through the sphenoidal fissure. These are the ophthalmic veins, the 3rd, 4th and 6th motor nerves which innervate the muscles controlling eye movement, and the sensory branches of the upper division of the 5th nerve, connected with the cornea, conjunctiva, lids, &c. In order to allow the eye free movement, the surrounding structures form with it a ball-and-socket joint. The joint cavity is formed by a pouch-shaped structure called the capsule of Tenon. This pouch surrounds the posterior four-fifths of the eyeball, in fact its folded margin touches the ocular conjunctiva. The pouch is made of a tough smooth membrane, and contains synovial fluid so as to allow the eye the greatest freedom of movement. Since the six muscles which cause the eye movements are attached to the bony wall of the orbit behind and to the front portion of the globe in front, it is clear that the tendons of the muscles must pierce the capsule. This is done in a very admirable manner, so as to allow free movement and at the same time to prevent escape of synovial fluid. Moreover the edges of the apertures, through which the tendons enter, form strong bands which are attached to the bony walls of the orbit. These bands act as check ligaments, preventing excessive movement on the part of the muscles. Tenon's capsule contains numerous smooth muscle fibres which are innervated by sympathetic nerves from the cavernous plexus, *via* the ciliary (lenticular) ganglion and the long ciliary nerves. Stimulation of the nerves described causes contraction

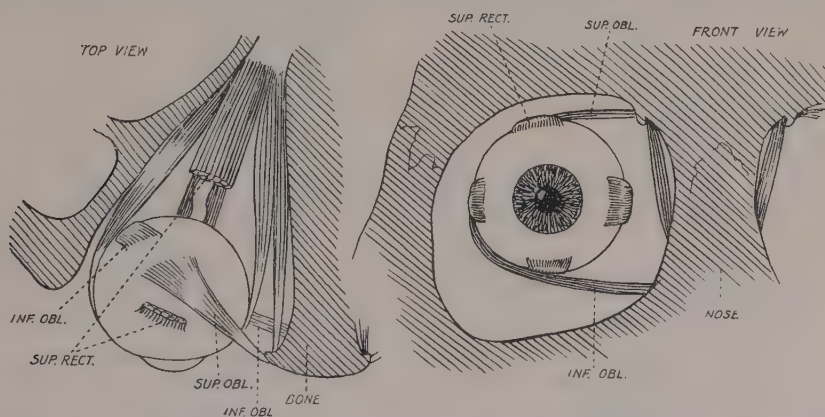


FIG. 213. The Anatomical Position of the External Muscles in respect to the Eyeball.

of these muscle fibres, protrusion of the eyes and rise of intraocular tension. But the most important function of these fibres is that by their tone they prevent the eye from being dragged back into the socket by the contraction of the external muscles. One of the explanations of the protrusion of the eyes in exophthalmic goitre is given to be the stimulation of the sympathetic nerves in the neck by the local pressure of the thyroid tumour, and it is said that removal of the superior cervical ganglion relieves the condition.

With regard to the position of the centre of rotation of the eye, it might be thought that, since the eye forms a ball-and-socket joint, the centre of rotation would be at the geometrical centre of the eyeball. Careful measurement shows that such is very nearly the case. The range of rotation of the eyes is considerable, being 88 degrees in a horizontal and 80 degrees in a vertical plane. If the sphericity of the globe of the eye is destroyed through disease, myopia for example, it is found that rotation is impaired.

ANATOMY AND FUNCTION OF THE EXTRINSIC MUSCLES OF THE EYEBALL

The six external ocular muscles produce rotation of the eyeball; four are called recti and two oblique. The recti arise from a fibrous ring attached to the margin of the optic foramen, and pass forward to meet the eyeball at its equator, where they form tendons. These having passed through Tenon's capsule are attached to the sclera about 6 mm. behind the corneal margin. From the positions they occupy they are called superior, inferior, external and internal. When they contract they will cause upward,

downward, outward and inward rotation of the eyeball respectively. In the case of the first two muscles there is a turning movement inwards at the same time; this is due to the muscle attachment round the optic foramen being on the inner side of the back of the orbit, since the muscles can cause rotation only in the directions which their tendons take. In addition to the above movements, and for the same reasons, there is a very small amount of rotation of the eye about the visual (antero-posterior) axis in the case of the superior and inferior recti, the directions in both cases being obvious from the directions of the pull of the muscles. Figs. 213 and 214 show the above diagrammatically. The two oblique muscles, the superior and inferior, are both smaller than the recti. The former arises near the optic foramen, and passes forward to the upper and inner side of the orbit, forming on its way a round tendon. It here passes through a narrow fibrous ring, and then turns downwards and backwards under the superior rectus and becomes attached to the eyeball nearly opposite to the attachment of the superior oblique. On contraction of the superior oblique the upper side of the eye is rotated towards the nose; at the same time the pupil is directed slightly downwards and outwards. The inferior oblique also causes rotation about the visual axes, but in the opposite direction; it at the same time produces upward and outward movement of the pupil. The function of these two small muscles appears to be to prevent the eyes from rotating about their visual axes, and in particular to prevent the rotation inwards which is associated with the contraction of the superior and inferior recti. For this purpose the superior rectus is associated with the inferior oblique and

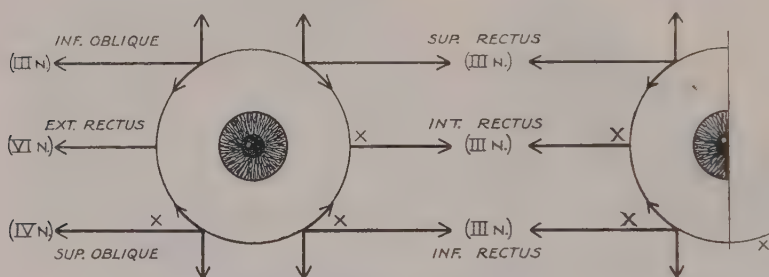


FIG. 214. Diagram showing the Directions in which the different Extrinsic Eye Muscles rotate the Eyeball. *x* = crossed connection.

vice versa. In this action the oblique muscles appear to be very efficient; for if the eye is first fatigued by looking at a brilliant line of light, *e.g.* a long straight electric lamp filament, and is then directed upwards or downwards at a white surface, the after image thus produced is always found to keep its vertical direction.

On tilting the head suddenly about a transverse axis, it is found that the eyes rotate in the opposite direction, so that in fact the image formed on the retina shall still keep in the same apparent meridian. This rotation is called compensatory, and is largely effected by the oblique muscles.

CO-ORDINATED MOVEMENTS OF THE EYES

The notable feature of the eye movements is the close association which exists between the muscles of the two eyes. For so perfectly has this mechanism been developed that the eyes are able to glance rapidly from place to place without there being any obvious doubling of the images. The eye movements are therefore of such a kind that the image of an object conveys a single impression to consciousness. But objects vary in the distance at which they are placed and therefore, beside movements of the eyes in which the visual axes remain parallel, there are also movements in which there is a certain amount of convergence. In the latter case there is usually some associated accommodation of the lens for near objects, and at the same time some contraction of the pupil. By experiments in which prisms are placed in front of the eyes, thus calling for convergence or divergence without accom-

modation, and by others in which lenses are placed there instead, thus requiring accommodation without change in the angle between the axes, it can readily be shown that the association between the functions of accommodation and convergence is not very rigid. The co-ordinated deviations of the eyes appear to be much more closely connected. Thus Donders found co-ordinated deviations both in the newly born and in congenital blindness. This is probably due to the close anatomical relationship which exists between the nerve centres of the muscles on the two sides. This has already been dealt with in Chapter XVIII., p. 297.

3.—THE STRUCTURE OF THE EYEBALL

The eyeball is a sphere, about 20 mm. in diameter. It lies near the front of the orbital cavity protected by the eyelids. The greater part of its external surface is formed

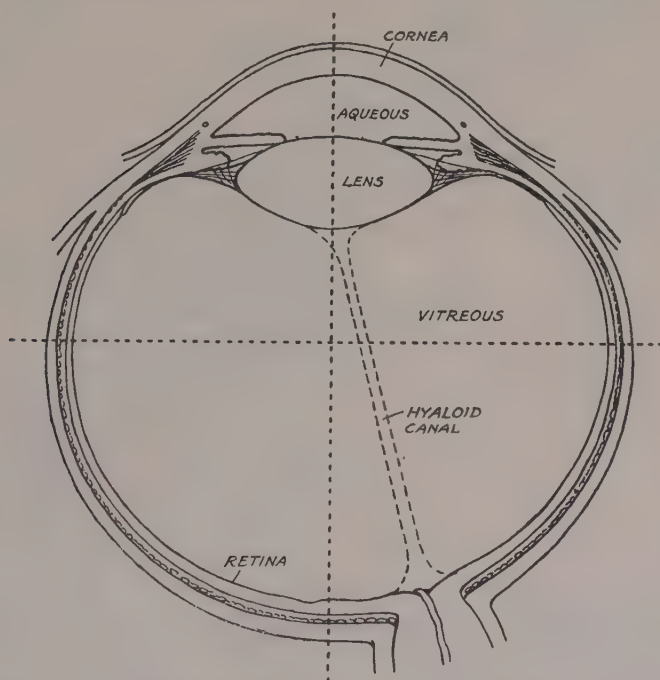


FIG. 215. Transverse Section through Equator of left Eye seen from above.

by a firm white membrane called the sclera. In front this is replaced by a transparent structure called the cornea. This has a greater curvature than the rest of the eye, the radius of its surface being about 8 mm. Attached to the eyeball behind and slightly to the inner side is the optic nerve, the function of which is to convey to the brain the light impressions received by the eye. Attached to it also, about 6 mm. from the corneal margin, are the tendons of four of the ocular muscles, as described on p. 385. The sclerotic is lined within by a highly vascular and deeply pigmented coat called the choroid. In front this coat has a circular aperture, in relationship with which the choroid becomes modified into several important structures, namely the iris, ciliary muscles and ciliary glands. Spread out within the hollow cup formed by the sclera and choroid is a soft delicate membrane of nervous tissue, the retina, which is connected with the optic nerve. The spherical cavity thus formed is entirely filled by three transparent structures, the lens, the aqueous humour and the vitreous humour. The lens is a biconvex body of high refractive index, which is situated symmetrically behind the opening in the iris, being held in place by the suspensory ligaments. The aqueous humour is the fluid which fills the cavity in front of the lens, while the semi-solid vitreous humour fills the cavity behind it. The eye is therefore a solid organ having considerable rigidity.

MINUTE ANATOMY OF THE EYE. THE CORNEA forms the transparent anterior convex front of the eye. Its curvature has a radius of nearly 8 mm. and a diameter of 11 mm. Its thickness is 1.1 mm., and is composed of the following five layers: (1) Stratified epithelium continuous with that covering the conjunctiva. Superficially the cells are nucleated squames, deeply they are nucleated columnar cells, and the layers between are a gradual transition from one type to the other. (2) The anterior elastic lamina of Bowman. This is not true elastic tissue, but a layer of modified substantia propria. (3) Substantia propria which consists of a special type of fibrous

connective tissue. The fibres are arranged in parallel rows to form laminae, and the laminae are built one above the other, leaving cell spaces or lacunae between. The fibres of each lamina are cemented together by an amorphous substance of nearly the same optical density, so that the laminae form one homogeneous structure. It is on this arrangement that the transparency of the cornea depends. If an excised eye be squeezed so as to produce a high intraocular tension, the cornea is seen to become partially opaque. This is caused by the tension in the corneal fibres making them become doubly-refracting. But owing to this double refraction the laminae of the cornea cease to form one homogeneous structure, and therefore opacity is the result. Within the lacunae are to be found the corneal corpuscles, which are flat nucleated star-shaped cells. (4) The posterior elastic lamina of Descemet. This is a clear structureless membrane which splits at its periphery into three layers. The first enters the sclera, the second gives attachment to the ciliary muscle, while the third enters the iris as the ligamentum pectinatum iridis and gives attachment to it; the intervals between its fibres are called the spaces of Fontana. (5) A layer of epithelium. This consists of a single layer of flat nucleated cells which line the spaces of Fontana and the anterior surface of the iris.

The cornea is nourished during health by a flow through the cell spaces, of lymph which comes from the peripheral vessels. During its development, and when diseased, it is supplied by capillaries which run in from its edge. Its sensory nerve supply is extremely rich, but pain end organs alone appear to be present.

Histologically the sensory nerve filaments are found to ramify actually in the surface layers of the stratified epithelium, a condition not found in any other part of the body. This arrangement and the acute pain response, which even the smallest foreign body can initiate, obviously has for its

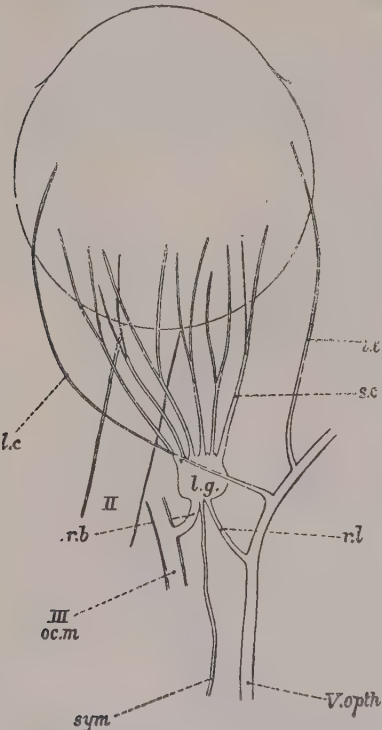


FIG. 216. Nerve Supply to the Eyeball.
(After FOSTER.)

- l.g.* Lenticular ganglion with its three roots, viz:
r.b. Radix brevis or short root.
r.l. Radix longus or long root.
sym. Sympathetic root.
V. ophth. Ophthalmic division of V. nerve.
III oc.m. Oculo-motor nerve.
II. Optic nerve.
l.c. Long ciliary nerves.
s.c. Short ciliary nerves.

object the protection of this important surface from injury. The pain impulses are conveyed to the brain either via the perichorioidal nerve plexus and the long ciliary nerves to the nasal branch of the 1st division of the 5th nerve, or from the plexus by the short ciliary nerves to the ciliary ganglion, and from this through the radix longa to the nasal nerve. In either case the nerves appear to have their cell stations in the Gasserian ganglion.

THE SCLERA, which forms the tough shell of the eyeball, consists of three layers: (1) a thin layer of endothelium in contact with the capsule of Tenon; (2) the loose episclera; (3) numerous interlacing bundles of white fibrous connective tissue; (4) a layer of flat endothelial cells and a network of fine pigmented connective tissue cells, forming the lamina fusca.

Beside the optic nerve, the sclera is perforated by the short and long ciliary nerves and by the ciliary arteries. The four venæ vorticosæ leave it at the equator. At the corneo-scleral junction the two structures are continuous. A space is left, however, which forms a ring round the cornea. This is called the canal of Schlemm; it communicates with the anterior chamber through the spaces of Fontana and also with the scleral veins. The presence of these canals renders the sclero-cornea weak and therefore liable to be ruptured by violence.

THE CHORIOID forms the vascular and pigmentary lining of the eye. It intervenes between the sclera and the retina. Histologically it consists of three layers: (1) the lamina supra-chorioidea, which is similar in its structure to the lamina fusca of the sclera: (2) the lamina propria which consists of connective tissue, richly supplied with blood vessels, capillaries, veins and nerves: (3) the basilar membrane of Bruch. This is a thin transparent structureless layer like that of Descemet in the cornea.

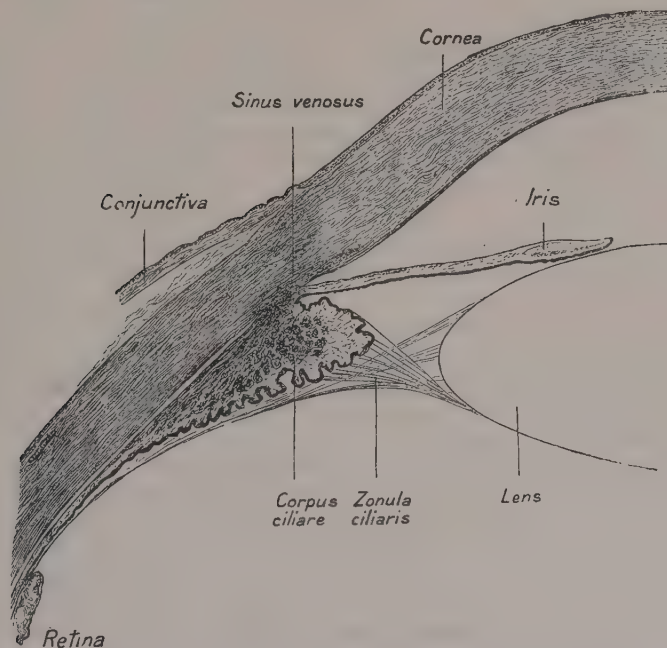


FIG. 217. Section through Anterior part of Eyeball to show Relations of Iris and Ciliary Bodies to Corneo-scleral Junction and Lens.

A highly reflecting surface, called the tapetum, is present in certain animals. This is formed by a layer of iridescent cells in the lamina propria.

THE CILIARY BODY connects the chorioid to the iris. It consists of three parts: (1) the ciliary muscle, the function of which is to cause the accommodation of the lens; (2) the ciliary glands which secrete the aqueous humour; and (3) the orbiculus which is the part of the ciliary body connecting it with the chorioid. The ciliary bodies are covered by a thin pigmented layer which is a continuation of the retina. This also covers the posterior surface of the iris and ends there.

THE IRIS consists of three layers: (1) the endothelium, continuous with that on the posterior surface of the cornea; (2) the stroma of the iris, which consists of connective tissue (especially elastic fibres), two thin sheets of muscle, some pigment cells, vessels and nerves; (3) the pigmented layer continuous with the retina.

It should be noted that the posterior elastic lamina of Descemet in the cornea, after its division into three parts, forms by its posterior portion the ligamentum pectinatum iridis, by which the iris gains attachment to the sclero-corneal junction.

THE FUNCTIONS OF THE IRIS. The iris contains two layers of unstriated muscle fibres; the anterior, which is circularly arranged, so that by its contraction it acts as a sphincter; while the posterior is arranged radially, stretching from the attachment of the iris to the rim of the pupil, so that by

its contraction it causes the pupil to open. Because of the numerous pigment cells which it contains the iris is opaque to light. Contraction of the pupil thus causes the following effects : (1) reduction in the amount of light entering the eye, so that an image of less intensity is formed on the retina ; (2) the use of the more central zones of the lens system only. The advantage of this lies in the fact that, as will be described later, the more peripheral zones suffer from errors of refraction to a much greater degree than do the central ones : the contraction of the pupil therefore improves the definition of the image ; (3) an increase in the depth of focus of the eye, which is of great value for near vision. The way that depth of focus is obtained will be described later (see page 409).

CONTRACTION OF THE PUPIL occurs under the following circumstances :

(1) When light falls on the retina. This movement, which is known as the 'light reflex,' is determined by a contraction of the sphincter pupillæ, together with a relaxation of the dilator muscle. The contraction ensues within a period of 0.04 to 0.05 sec. after the moment at which the light has access to the retina, and attains its maximum within 0.1 sec. In man as well as in other animals which have binocular vision, and in which there is a partial decussation of the fibres of the optic nerves in the optic chiasma, the reflex is bilateral, *i.e.* light falling into one eye causes simultaneous contraction of both pupils. In the higher animals this reaction of the pupil to light demands the integrity of the nervous paths between the eye and the brain ; but in many of the lower animals, *e.g.* in the frog and eel, the reflex nervous mechanism is aided by a local sensibility of the iris to light. In these animals the contraction of the pupil in response to illumination takes place even in the excised eye, and seems to be determined by a direct stimulation of the pigmented contractile fibres of the sphincter pupillæ by means of the light.

The effect of light on the pupil varies considerably according to the condition of adaptation of the eye. The dilatation of the pupil is maximal when the eye has been in the dark for some time and may amount then to 7.3 to 8 mm. In one experiment, on exposing the eye to a feeble light, *e.g.* 1.6 candles at a moderate distance, the pupil diminished in size to 6.3 mm. ; with an illumination of 50 to 100 candles the size of the pupil was 3.7 mm., and with 500 to 1000 candles, 3.3 mm. This effect was obtained by a *rapid* change in the illumination of the eye. When the alteration is sudden, the amount of contraction was found by Haycraft to be equal to the logarithm of the intensity of the light. When, however, the alteration is so gradual that the retina can become adapted to the change as it proceeds, then little or no change in the size of the pupil occurs ; and when the illumination, which has at first caused a maximal constriction of the pupil, is continued, the pupil gradually relaxes with the adaptation of the retina to light. This relaxation occurs within three or four minutes after exposure to light has taken place. The same influence of adaptation will be observed if two individuals are brought into a moderately lighted room, one from bright daylight and the other from a dark room. The pupils of the first will dilate widely, while those of the second will constrict to their maximum extent. In each case the change will pass off regularly, so that at the end of five or ten minutes there will be no difference observable between the eyes of the two persons.

(2) When vision is directed to a near object, the functions of accommodation of the lens, and of convergence of the visual axes, which result, are associated with contraction of the pupil. The sharpness of vision is thereby improved, together with an increase in the depth of focus, a

result very beneficial for the close examination of detail. Since it is possible by experiment to cause accommodation without convergence and *vice versa*, we may ascertain which function is the more closely associated with the pupil mechanism. The evidence appears to be in favour of convergence.

(3) In sleep the pupils are always contracted. This behaviour may enable us to distinguish feigned from real sleep. This contraction of the pupils, in spite of the fact that no light is entering the eyes, has been held to be caused by association with the upward and inward direction of the eye axes which was said to be found in sleep. There now appears to be irrefutable evidence that the eyes during sleep may occupy any position; another explanation of the constricted pupils must therefore be found.

(4) Contraction of the pupils is a marked effect of certain drugs such as opium, or the alkaloid morphine; other examples are pilocarpine, muscarine and physostigmine. The parts of the pupillo-motor mechanism on which these drugs act will be considered later (see page 392).

(5) Constricted pupils are also met with in excitable conditions of the central nervous system, and therefore during the induction of chloroform and ether anæsthesia.

(6) Small pupils, which do not react to light, are also met with in injuries to the spinal cord involving the cervical region. The explanation of this will be given later (see page 392).

(7) Contracted pupils are found to accompany agony. This is probably due to the powerful flow of efferent impulses which leave the brain in this condition, affecting the 3rd nerve nucleus which controls the pupil.

(8) The pupil contracts when the aqueous is allowed to escape from the anterior chamber. The cause of this is said to be the dilatation of the vessels of the iris, owing to the fall of the surrounding pressure.

DILATATION OF THE PUPIL. (1) Occurs on removal of a light stimulus from the eyes. If the removal be complete the pupil remains dilated, but if there be any light at all the pupil gradually contracts again as the eye becomes dark adapted.

(2) Occurs on accommodation for distant vision because the associated reflex stimulation of the pupillo-motor centre with accommodation is no longer called into play.

(3) Reflex dilatation of the pupil can be excited by the stimulation of any sensory nerve. This may be due to some of the afferent impulses reaching the cilio-spinal sympathetic nerve centre in the cord.

(4) The pupils are frequently found to dilate in such emotional states as fear, anxiety, exhaustion and dyspnoea, and also at the moment of death.

(5) Dilatation is also found to accompany extreme exhaustion of the central nervous system, when the activity of all nerve centres is low, such as in deep chloroform anæsthesia, and in the coma produced by alcohol poisoning. Many other drugs such as atropine and homatropine, cocaine and adrenaline cause dilatation, as will be described later.

(6) Dilated pupils inactive to light are found in injuries of the 3rd nerve or its nucleus.

(7) Dilated pupils are also found when the intraocular pressure is abnormally high, as in glaucoma. This appears to be due to constriction of the vessels of the iris owing to the high external pressure to which they are subjected.

(8) Dilated pupils inactive to light are found in compression and severe

concussion of the brain. This is probably due to the abolition of the normal nervous impulses to the muscles, so that the pupil dilates under the influence of its radial elastic fibres.

(9) Dilated pupils are found to accompany hyperactivity of the supra-renal glands, owing to the presence of considerable amounts of adrenaline in the blood. This occurs for example in oxygen want, dilated pupils being one of the characteristic signs of that condition.

ACTION OF DRUGS. The following Table shows the action of certain drugs on the pupil.

TABLE TO SHOW ACTION OF DRUGS ON PUPIL.

Name of drug.	Pupils.	Action.
Morphia . . . } Opium . . . }	Small	Stimulate 3rd nerve nucleus.
Pilocarpine . . } Physostigmine . } Eserine . . . }	„	Stimulate 3rd nerve endings in sphincter pupillæ.
Chloroform . . } Ether . . . }	„	At first act like morphia. In larger doses cause paralysis and therefore large pupils.
Atropine . . . } Homatropine . }	Large	Paralyse 3rd nerve endings in sphincter pupillæ.
Adrenaline . . . } Cocaine . . . }	„	Stimulate the sympathetic nerve endings in the radial muscle fibres.
Curare } Nicotine . . . }	Small or Large	By paralysing the synapses in the ciliary or superior cervical ganglia if painted on them.

THE SPHINCTER. This muscle is supplied by nerve fibres which arise from the upper portion of the 3rd nerve nucleus in the ventral part of the Sylvian grey matter (see Fig. 165). They travel down in the nerve as far as the ciliary (or lenticular) ganglion which is situated behind the eye close to the optic nerve. Here a branch from the nerve enters the ganglion to anastomose with its nerve cells. These nerve cells send off numerous small nerves called the short ciliary nerves (Fig. 216) which enter minute apertures in the sclera arranged in a ring round the optic nerve. Having entered the perichorioidial lymph space, the nerves form a plexus from which are supplied the local blood vessels, the ciliary muscle and the sphincter of the pupil.

THE DILATOR. This muscle of the iris is supplied by nerve fibres which originate in nuclei situated near that part of the 3rd nerve nucleus which supplies the sphincter fibres; this must be the case in order to explain the reciprocal innervation of the two antagonistic sets of muscles. From these nuclei, nerve fibres travel down the cord as far as the 8th cervical and 1st dorsal ventral nerve roots, with which they leave the cord. They then proceed as part of the white rami communicantes to the superior thoracic

ganglion, and thence by the sympathetic chain to the superior cervical ganglion, with the cells of which they anastomose. From these nerve cells the terminal nerve fibres for the dilator muscle of the iris arise. They appear to travel by two distinct routes : (1) from the superior cervical ganglion to the Gasserian ganglion of the 5th nerve, along the nasal branch of its 1st division, turning off with the two long ciliary nerves to end by entering the sclera and joining the perichorioidal plexus, and thence to the dilator muscle ; (2) from the superior cervical ganglion grey rami are given off which travel with and form plexuses on the various branches of the internal carotid artery. One of these is the cavernous plexus which sends a fine branch to the ciliary ganglion. From here the fibres travel with the short ciliary nerves as already described.

It is clear, therefore, that the short ciliary nerves contain both pupil constrictor (3rd nerve) and pupil dilator (sympathetic) fibres so that, when

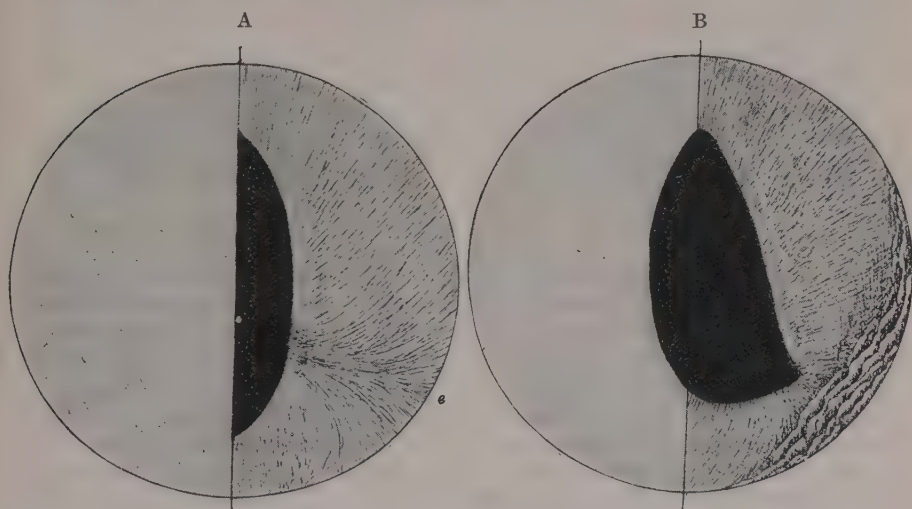


FIG. 218. Effect of Local Stimulation on Iris of Cat.

The first effect, as in A, is to cause contraction of the constrictor pupillæ below the electrodes, and this is succeeded in B by a strong localised contraction of the radiating fibres. (LANGLEY and ANDERSON.)

these nerve fibres are stimulated electrically, both the sphincter and the radial muscles of the iris will contract. But the sphincter fibres being the more powerful will overcome the others and therefore cause contraction of the pupil.

The nerve paths above described, and the effects on the pupil which excitation of the nerves produces, have been ascertained by the employment of the well-known methods of cutting the nerves, stimulating the cut ends, and also by following the tracts marked by degeneration. Thus cutting the sympathetic anywhere causes contraction, while cutting the 3rd nerve produces dilatation. Stimulation of the peripheral cut ends causes the opposite effects. The course of the dilator impulses down the cord to the cervico-dorsal region explains the contraction of the pupil which sometimes accompanies injuries to the cervical spine, and explains the origin of the term cilio-spinal centre.

Since the dilatation of the pupil is accompanied by contraction of the radial fibres on the one hand, and inhibition of the sphincter fibres on the

other, and *vice versâ* when contraction takes place, it would seem almost necessary to assume that there is some system of reciprocal innervation, like that found by Sherrington in the case of the limbs. Experimental evidence would point to such being the case. Thus stimulation of a part of the sensori-motor area of the brain is followed by dilatation of the pupil, which occurs even when the sympathetic has been cut. Since this excludes the possibility of an active contraction of the radial fibres (their nerve supply having been cut), it appears to prove that a reciprocal inhibition of the sphincter has been produced. The existence of this reciprocating mechanism must greatly increase the efficiency with which the pupil works.

The above experiment also shows that there is a connecting nerve path between the pupillo-motor centre and the cortex of the brain. The reaction of the pupil to light and the association which exists between pupil, accommodation and convergence indicate that there are a number of other important connections between the pupillo-motor and other centres. The more important of these will therefore be traced.

THE LIGHT REFLEX. This reflex in birds is to a considerable extent under voluntary control; but in man and in most other higher vertebrates the control is involuntary and unconscious, the size of the pupil being determined by the intensity of the light which is reaching the retina. The function of the pupil appears rather to protect the retina from any sudden change of intensity, than to control the actual intensity of the light.

With regard to the reflex arc, the connection of the iris with the pupillo-motor centre has already been described. The connections of the retina with this centre appear to traverse the following course. Starting from the retina on one side, the impulses travel up the optic nerve as far as the chiasma, where they travel on without decussating, and end by anastomosing with nerve cells in the anterior corpora quadrigemina. These nerve cells correspond with second order neurones and proceed to the pupillo-motor centres of both sides. It is found by experiment in monkeys that dividing the chiasma in the middle line does not stop the pupil reflex either in the eye stimulated or in the other eye. This shows that the nerves concerned with the light reflex go to the superior corpora quadrigemina of the same side, and that the consensual reflex is due to the fibres from each superior corpus quadrigeminum supplying the pupillo-motor centres of both sides. The appreciation of light by the retina is exceedingly rapid, whereas the response of the pupil to light action is very delayed. This is due in part to the fact that the muscles of the iris are composed of involuntary, smooth fibres. There is, however, a pathological condition called Hippius, in which the pupil alternately expands and contracts at a rate that would be impossible if the attempt were made to produce this effect by intermittently exposing the eye to light. This proves that the muscle fibres can react more quickly and therefore that there is somewhere in the reflex arc a delay action mechanism. The object of this mechanism would appear to be to render the pupil stable and to prevent 'hunting.' When this mechanism is diseased Hippius results.

The accommodation reflex has been already considered. The close anatomical association of the 3rd nerve centres for pupil sphincter, accommodation and convergence by the internal recti is shown in Fig. 172. When volitional impulses therefore come down from the frontal lobes of the cerebral hemispheres, they are conveyed to this group of centres, and the associated reflex results.

ARGYLL-ROBERTSON PUPIL. The diagnosis of interference with the pupillo-motor reflex is of considerable practical importance, because these paths appear to be particularly sensitive to the presence of certain specific toxins in the blood. The commonest type is one in which there is contraction of the pupil on accommodation, but little or no reaction to the stimulus of the retina by light. This condition of the pupil is called the Argyll-Robertson pupil. The seat of the injury appears to be either in the fibres travelling from the retina to the superior corpus quadrigeminum or in those coming from these centres and travelling to the 3rd nerve nucleus.

4.—THE NOURISHMENT AND PROTECTION OF THE EYE

ANATOMY OF THE LIDS. Closing the orbit in front, and in close relationship to the eyes, are the lids or palpebræ. The upper, which is the larger and the more movable, is provided with a special muscle, the levator palpebræ superioris. This is supplied by a branch of the oculo-motor (3rd) nerve. The two lids meet at an angle on both sides, forming the inner and outer canthi. They are stiffened by two plates of dense fibrous tissue, parallel to their edges, which are called tarsi. Near these and embedded in the substance of the lids are two sets of glands, the Meibomian glands and those of Moll. These secrete a greasy material which spreads over the lids. Superficial to these structures, but under the skin, is a ring of muscle fibres which is common to both lids, the orbicularis palpebrarum, innervated by the 7th nerve. Its contraction closes the lids. Lining the inner surfaces of the eyelids is a thin layer of mucous membrane, the conjunctiva, which is reflected on to the front of the eye, and is continuous over the cornea as the anterior epithelial layer.

CLOSURE OF THE LIDS occurs : (1) during sleep ; (2) if a very bright light enters the eyes ; (3) on the sudden approach of some foreign body ; (4) on contact of a foreign body with the lashes ; (5) on irritation of the cornea or conjunctiva ; (6) in sneezing ; (7) in order to renew the fluid film on the cornea and conjunctiva. The reflex closure of the lids is therefore a very important function in affording protection to the eyes. The reflex apparently can be initiated by the stimulation of any of the branches of the ophthalmic (1st) division of the 5th (trigeminal) nerve. From the nucleus of this nerve in the pons Varolii, fresh fibres take the impulses, it is believed, to the 3rd nerve nuclei of both sides. The fibres leave the 3rd nerve, however, and join the 7th (facial) nerve, from which they pass to the orbicularis palpebrarum. This reflex is one of the last to be abolished by anæsthetics and is therefore used as a convenient test. It is called the *conjunctival reflex*.

The conjunctivæ and the cornea are kept in a moist condition by the tears, which are secreted by the lachrymal gland, situated in the upper and outer part of the orbit. This is a small acino-tubular gland, in microscopic structure similar to the parotid. Its secretion issues through several ducts, the mucous linings of which are continuous with that of the conjunctiva. Normally the secretion is just sufficient to keep the surfaces of the lids and cornea moist, the production keeping pace with the evaporation. Under certain circumstances there is excess, and tears are produced.

TEAR FLUID consists chemically of an aqueous solution of sodium chloride and bicarbonate containing mucus, albumin and *débris*. It is found to have a bactericidal power, which is lost if the fluid is boiled. Its functions are to keep the surfaces of the conjunctiva and cornea moist, and to remove foreign bodies and organisms. The secretion of tears is increased (1) by irritants and foreign bodies coming in contact with the cornea, conjunctiva or lids ; (2) by irritation of the nasal mucous membrane ; (3) by powerful illumination of the eyes ; (4) by the incidence on the eye of infra-red (heat) or ultra-violet (actinic) rays ; (5) under the influence of emotion.

When excessive tear formation occurs, the fluid either escapes over the front of the lids or is drained away through the lachrymal duct into the nasal sinus. Three theories have been advanced to explain the latter: (1) syphoning, owing to the mouths of the ducts being at a higher level than their exit into the nose; (2) capillarity, owing to the tendency of the liquid to flow into the ducts through surface tension; (3) active removal by the act of blinking. It is not at the present time definitely known how this occurs. Some say that on closing the eye the internal palpebral ligament tends to be pulled on, and that this dilates and fills the lachrymal sac; others that the sac fills automatically through having been previously

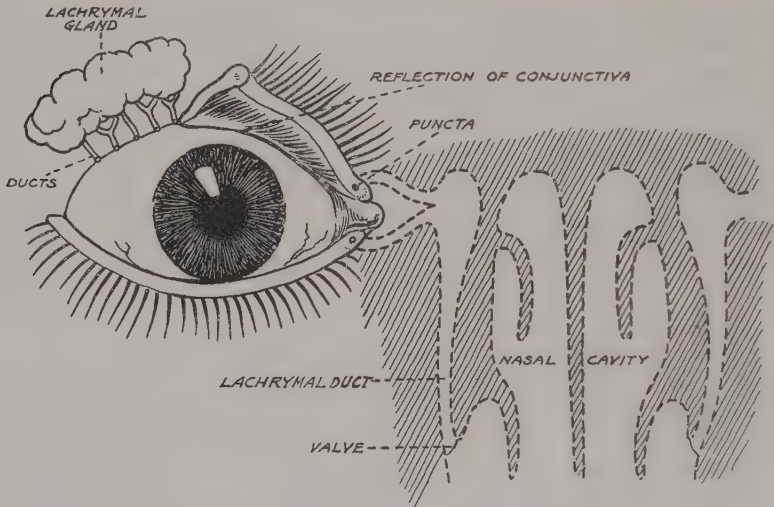


FIG. 219. Diagram to show Origin and Fate of Tear Fluid.

emptied by the contraction of Horner's muscle. It is possible that both processes occur.

The eyes of some mammals and fish and nearly all birds are provided with a nictitating membrane, a semi-transparent shutter which can be brought over the surface of the cornea. In the fish its possible function is to prevent the irritation of fine sand particles when swimming in rough water, without at the same time disturbing vision. In the case of the bird it might be used (1) to moisten the cornea during flight without interrupting vision; (2) to reduce the light intensity when flying at high altitudes or when travelling towards the sun; (3) to reduce the irritation caused by ultra-violet or infra-red rays which are present in excessive amount at high altitudes.

NUTRITION OF THE EYE

The eyeball is richly supplied with blood vessels, which form numerous anastomoses. Among these may be mentioned the arteries of the optic nerve sheath, the long and short posterior ciliary arteries, the anterior ciliary arteries, which are branches from the muscular vessels, and the conjunctival arteries. These pierce the sclera to ramify freely in the chorioid and in the ciliary bodies. The iris is supplied by two concentric vessels, the *circulus major* and the *circulus minor*. Between the two pass a number of radial fibres. The retina has a separate blood supply through the central artery of the optic nerve. Other structures, notably the transparent optical media

of the eye, have no direct blood supply and therefore depend on the flow of lymph from neighbouring structures for their nutrition. This fluid is formed principally by the ciliary bodies, and is called aqueous humour.

AQUEOUS HUMOUR. The chemical composition of this fluid is water containing salts, traces of albumin and globulin, and a reducing sugar; it is probably freely oxygenated. This fluid after secretion leaves the eye in one of three ways. (1) By travelling through the pupil into the anterior chamber of the eye and then through the spaces of Fontana at the edges of the iris (the so-called filtration angle) into the canal of Schlemm and thus into the ciliary veins. (2) Through the crypts in the anterior surface of the iris into the veins of that structure. (3) Between the suspensory ligaments of the lens to the anterior surface of the vitreous, then down the hyaloid canal to the papilla of the optic nerve, and thus out *via* the lymphatics of the nerve sheath or the retinal vessels. But whatever the fate of the liquid may be, it is certain that the amount secreted must be the same as that which leaves, because otherwise there would be a variation in the intraocular tension. Insufficient pressure will tend to disturb the correct relationship between the internal structures of the eye, and at the same time will prevent the proper action of the ciliary muscle in causing accommodation, because the suspensory ligaments of the lens will already be relaxed. Too great a tension on the other hand will interfere with the proper blood supply to the eye, and will prevent accommodation because the tension in the choroid will be too great for the ciliary muscles to overcome (see page 406). It is therefore important that there should be a proper control of the intraocular pressure. Experiments by Henderson and Starling, in which the intraocular pressure was determined by a null method (Fig. 222), showed that such a mechanism exists, because as the arterial pressure increased so also did that in the eyeball.

Whereas the arterial pressure varied between 70 and 180 mm. (*i.e.* a

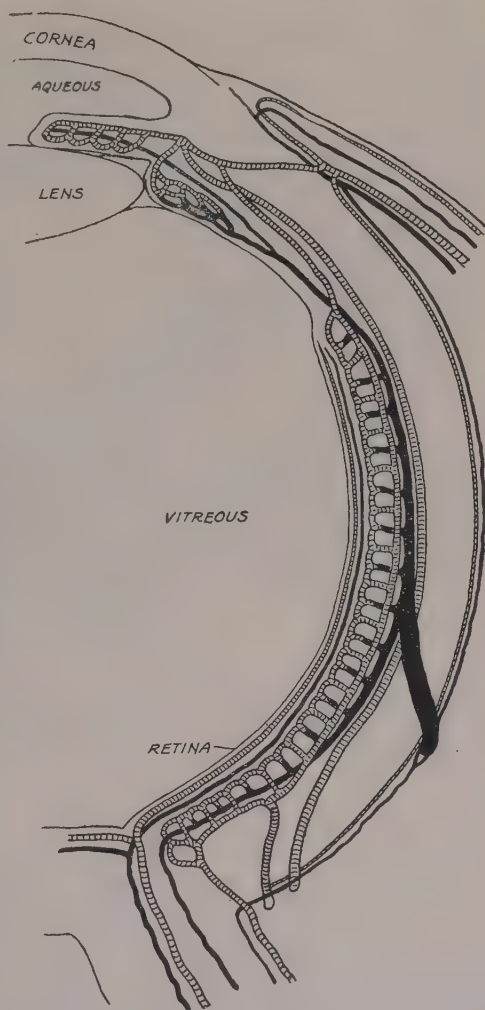


FIG. 220. Diagram to show the Blood Supply of the Eyeball. Arteries 'lined,' veins 'black.'

difference of 110 mm.) the intraocular pressure was found to vary between 23 and 40 mm. (that is by only 17 mm.). The change in intraocular tension is therefore less than one-sixth of that taking place in the blood; the control mechanism would therefore appear to have very considerable efficiency.

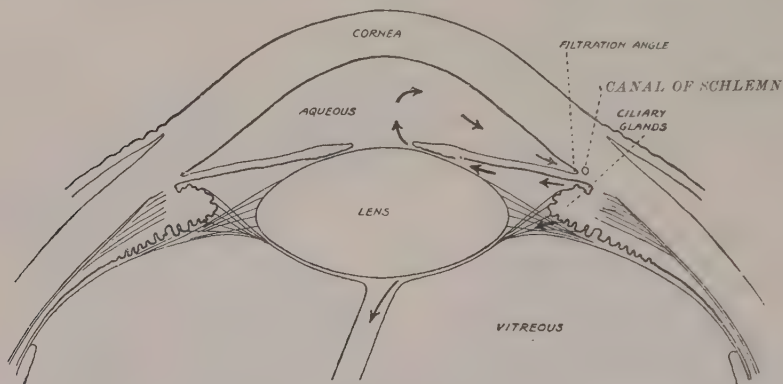


FIG. 221. Diagram showing Origin and Fate of Aqueous Humour.

GLAUCOMA. The normal intraocular pressure in man is found to be between 25 and 30 mm. of mercury. The tension thus set up in the walls of the eyeball is principally borne by the sclera; to some extent however assistance is rendered by the chorioid owing to its elasticity, and by Tenon's capsule owing to the tonic contraction of its smooth muscle fibres (innervated by the sympathetic).

In abnormal conditions the efferent channels may become closed, either from pressure.

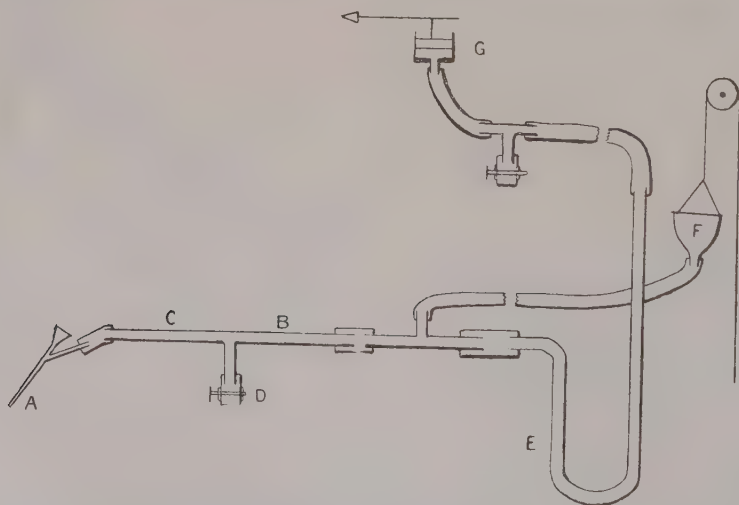


FIG. 222. Arrangement of Apparatus for Measurement of Intraocular Pressure. (HENDERSON and STARLING.)

G is a piston recorder for recording graphically the changes in pressure.

of the lens on the iris (as in hypermetropia) or from the presence of epithelial *débris* in the anterior chamber. The intraocular tension under these circumstances becomes very high, the disease being known as glaucoma. The principal symptoms of glaucoma are pain and impaired vision. The chief diagnostic signs are a stone-hard eyeball, sluggish, rather dilated pupils, and the retina when examined through the ophthalmoscope is found to show cupping of the optic disc, and vessels which are thin and show pulsation. In treating glaucoma, operative measures to lower the pressure should be

taken immediately, because the high pressure interferes with the proper blood supply to the eye. Since all hypermetropes (persons with long sight) have a tendency to suffer from glaucoma, care should be taken against giving drugs such as atropine which cause dilatation of the pupil, since this increases the resistance to the escape of fluid at the filtration angle, and therefore predisposes to an attack of glaucoma.

5.—THE OPTICAL SYSTEM OF THE EYE

The optical system of the eye consists of those structures which together focus on the retina an image of external objects. In the mammalian eye there are four concerned: the cornea, the aqueous humour, the crystalline lens and the vitreous humour. The histology of the cornea has already been considered. The aqueous humour is a structureless liquid. The vitreous

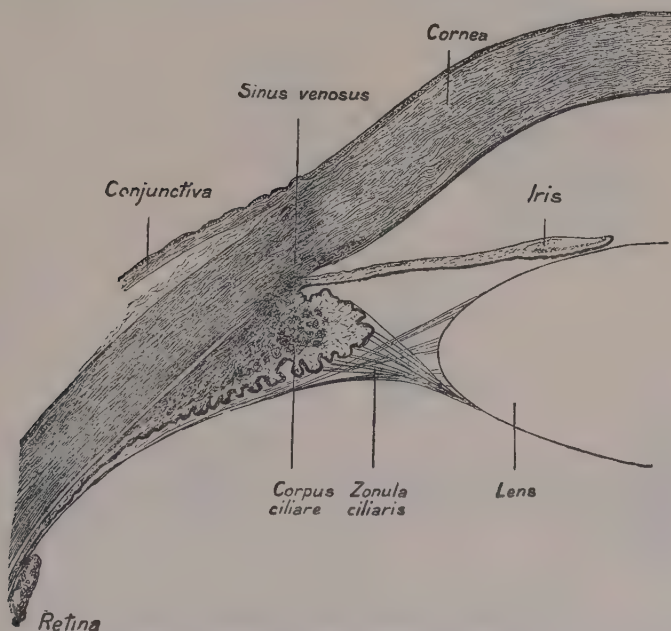


FIG. 223. Section through Anterior Part of Eyeball to show Mode of Suspension of Lens. (After MERKEL and KALLIUS.)

humour consists of anastomosing trabeculae of collagenous material, the interstices of which are filled by a slowly circulating fluid similar to aqueous humour. The vitreous is enclosed in the hyaloid membrane, and through the middle of it, during foetal life, runs the hyaloid artery, which goes from the central artery of the retina to the posterior surface of the lens.

THE CRYSTALLINE LENS is a biconvex transparent elastic body, enclosed in an elastic membrane called the capsule. To the periphery of the capsule are attached the suspensory ligaments of the lens, which are formed by the anterior radial fibres of the thickened portion of the hyaloid membrane (the zonula of Zinn) (Fig. 223). Between the suspensory ligaments are shallow pockets into which the ciliary processes fit closely. In this way the lens is held firmly in position, while at the same time by the movement of the ciliary processes under the action of the ciliary muscle, the traction can be altered in the suspensory ligaments, thus effecting the change in curvature of the lens, which will be shown later to be necessary for accommodation.

Histologically the lens is composed of a number of radially arranged fibres, each of which is a modified epithelial cell. These fibres are arranged in concentric layers, the more peripheral being soft, nucleated and of low refractive index, while the central form a dense non-nucleated mass of high refractive index, the fibrous layers between having an intermediate structure and index.

REFRACTION BY THE CRYSTALLINE LENS. Refraction occurs whenever light passes from one medium into another of different optical density. It is due to the fact that the waves, of which the beam of light is composed, travel more slowly in a dense medium than they do in one of less density. Some of the effects which this produces are shown in the diagram below.

At A, plane waves are seen entering a dense medium at an angle. At B the medium is lens shaped. At C the medium has a plane surface but

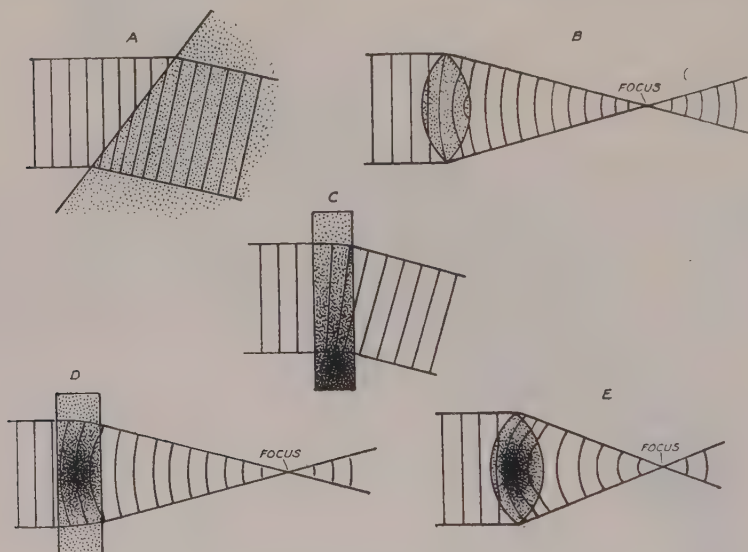


FIG. 224. Diagram showing Refraction of Light.

- | | |
|---|---|
| (A). By an inclined surface. | (D). By a plate of greater density at its |
| (B). By a lens. | centre than at its edges. |
| (C). By a plate of greater density at its | (E). By a lens of greater density at its |
| lower end than at its upper. | centre than at its edges. |

has a greater density below than above. At D the medium has a plane surface but a greater density at its centre than at its edges. At E the medium is lens shaped as at B, and also varies in density as at D. The very great refracting power of such a structure is well shown. This is the arrangement found in the lens of the eye, in which, therefore, the power of refraction is very much greater than that of an ordinary lens of the same curvature as the lens and the same refractive index as the average density of its substance. The optical properties of the lens are therefore unique, and it is interesting to find the same (*i.e.* even immunologically identical) protein in the lens of different morphological groups of animals.

To show the effect which the increasing density of the lens produces, the refractive indices of its parts may be compared with its equivalent R.I. (that is, the refractive index of a glass lens of the same size, shape and focal

length). The refractive index of the periphery of the lens is 1.37, and that of the central nucleus 1.41, the mean being about 1.39. But the equivalent density of the lens is found to be 1.42, that is, greater by 0.03 than the mean refractive index of its substance. The lens lies in contact with two transparent media, both of which have an approximate refractive index of 1.34. The power of the lens, if its composition were uniform, would therefore be proportional to the difference between its own mean R.I. (1.39) and that of its surroundings (1.34), that is to 0.05. Owing to its peculiar structure its equivalent R.I. is 1.42, and therefore its power is proportional to the difference between that and 1.34, that is to 0.08. Owing to its structure the lens has therefore increased in power in the ratio of 0.08 to 0.05. Now since the range of accommodation depends, other things being equal, on the power of the lens, we see that the peculiar structure of the lens has nearly doubled its range. The graduation in the densities of the different layers of the lens has a further advantage which will be described later,

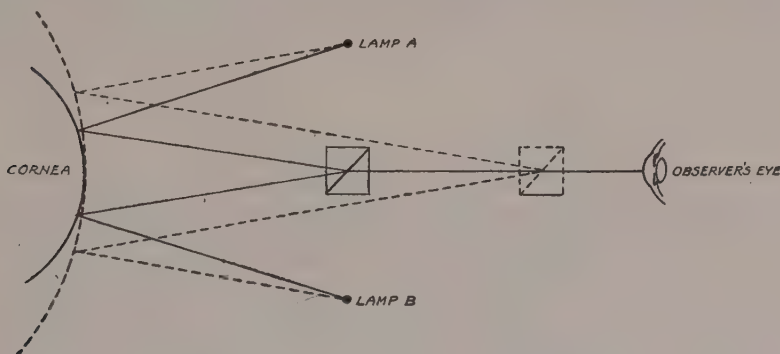


FIG. 225. Diagram to show a Method of Determining the Curvature of the Anterior Surface of the Cornea.

The images of the lamps A and B are caused to coincide by shifting the position of the double image prism. The greater the curvature of the cornea the closer must the double image prism be to the eye.

in that it reduces the spherical aberration of the eye as a whole and also reduces the amount of scattered light within the eyeball.

THE OPTICAL CONSTANTS OF THE EYE. In the case of the crystalline lens, two methods are available for the determination of the radii of curvature of the anterior and posterior surfaces, namely measurements on the excised lens, either in the air or preferably suspended in a fluid of known optical properties, or by estimating the apparent size of the images of an object which are formed by reflection at its surfaces. In order that the latter method shall succeed, a device must be employed for eliminating the effect of chance movements of the eye while under observation. This was first done by Thomas Young who employed a method used in astronomy, namely that of doubling the image to be measured and then adjusting the lower edge of one image to be in coincidence with the upper edge of the other. If the eye moved during the determinations, both images moved together and therefore difficulties in adjustment were avoided. In the case of the cornea this method is alone available because only in the living state is the true curvature preserved (Fig. 225). In the case of the lens the determinations are complicated by the fact that the refraction of the cornea has to be allowed for. Further, the images that are seen are neither bright nor sharply defined; but in spite of this considerable

accuracy is attainable. The following are the approximate values given by these methods.

Radius of cornea		8 mm.
Radius of lens, anterior surface		10 "
Radius of lens, posterior surface		6 "

THE REFRACTIVE INDICES (optical densities) of the eye media are determined on the excised eye by means of the Abbe refractometer. It is found that the cornea and aqueous are so nearly alike that for all practical purposes they may be regarded as one, particularly as the posterior corneal surface has nearly the same centre as the anterior. The refractive indices may therefore be given as follows :—

Refractive index of cornea and vitreous		1.34
Refractive index of lens (equivalent)		1.42
Refractive index of aqueous humour		1.33

THE APPLICATION OF GAUSS' THEOREM. In addition to the above data

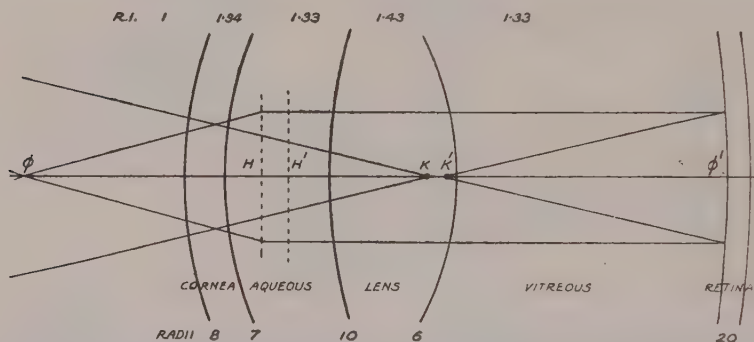


FIG. 226. The Optical System of the Eye shown diagrammatically.

H and H' principal points. K and K' nodal points. ϕ and ϕ' anterior and posterior foci.

we require to know the distance between the principal surfaces ; these are found to be :—

Distance from cornea to anterior lens surface		3.6 mm.
Distance from cornea to posterior lens surface		7.6 "
Distance from cornea to the retina		22.6 "

These values being known, it is possible by calculation to determine the path of any ray through the eye. The problem, however, is made very much simpler by the application of Gauss' theorem, which may be briefly stated as follows. Any system of spherical optical surfaces, the centres of which lie along a straight line, possesses six cardinal points, namely—two principal points H and H' (Fig. 226), two nodal points K and K', and two focal points, the anterior ϕ and the posterior ϕ' . It is found that these have certain properties which may be summarised as follows :—

An object placed at the first principal point is found after refraction to be at the second. Further, the image and its object are found to be of the same size. A ray passing through the first nodal point on its way into the system appears to come from the other on its way out, but its direction is still parallel to the path which it traversed initially. A ray passing through either focus leaves the lens system on the other side parallel to the axis. It is further found that the distances between some of these points are equal,

for example :— $\phi H = K'\phi'$ and $H'\phi' = \phi K$. Also $HH' = KK'$. The positions of these cardinal points has been determined in the case of the eye with considerable accuracy ; the following approximate values may be given :—

Distance from front of cornea to first principal point	H	1.7 mm.
Distance from first principal point to second principal point	H'	0.3 „
Distance from second principal point to first nodal point	K	5.0 „
Distance from first nodal point to second nodal point	K'	0.3 „
Distance from first principal point to anterior focus	ϕ	15.3 „
Distance from second nodal point to posterior focus	ϕ'	15.3 „
Distance from front of cornea to retina		22.6 „

The position of these points being determined, the direction of the rays of light through the eye can be easily obtained, and is shown diagrammatically in Fig. 226.

It is of some interest to know the relative part taken by the various refractive media of the eye in the formation of the image. By far the greater part is performed by the cornea. The following values in mm. and dioptries * may be given :—

	Mm.	Dioptries.
Focal length of the cornea	24	42
„ of the lens	44	23
„ of the whole eye	15.5	65

When opacities form in the lens (cataract) this structure is removed by operation. It is then found that a lens of approximately 10 dioptries has to be worn by the patient in order that he may see distinctly. To this a cylinder has usually to be added to correct astigmatism introduced into the eyeball from the scar of the incision ; and a 4-dioptre spherical lens has to be added when a glass for reading is being prescribed. If the glass lens could be placed inside the eyeball in the exact position occupied by the crystalline lens it would, as the above Table shows, require a power of 23 dioptries instead of 10 dioptries. When the eye is placed under water, the refraction of the cornea is necessarily abolished because water has approximately the same refractive index. Under these conditions the eye becomes too long-sighted for distinct vision. The eye of the fish has met this difficulty by the provision of a small, nearly spherical lens of very great density. In the fish, therefore, the lens takes the principal part in the refraction of the light in the formation of an image.

REDUCED EYE. It is a convenient fact that, owing to the closeness of the principal and nodal points to one another, it is possible to imagine the media of the eye replaced by a single optical surface without introducing any appreciable error. To this system is given the title 'reduced eye.' Its constants are given in the following Table :—

Radius of surface	5 mm.
Distance of principal point from anterior surface	2.3 „
Distance of nodal point from anterior surface	7.1 „
Distance of retina from anterior surface	22.6 „
Refractive index	1.33 „
Focal length	15.5 „

THE ACCOMMODATION OF THE EYE

The above description has been made on the supposition that the rays entering the eye consist of parallel bundles, or in other words that the objects

* In the dioptre nomenclature the figure represents the reciprocal of the focal length in metres. Thus 10 dioptries = $\frac{1}{10}$ metre = 100 mm. ; and 24 mm. = $\frac{100}{24}$ = 4.2 dioptries.

seen are at an infinite distance from the eye. But during near vision, such is by no means the case. If there were no means of varying the focus of the eye, it would not be possible for divergent rays (those coming from near objects) to be brought to a focus on the retina. The mechanism for varying the focus of the eye is called accommodation.

THE THEORIES OF ACCOMMODATION. Of these, three are of historic interest only. (1) That during accommodation the cornea increases in curvature (similar to the bird's eye). This was disproved by Thomas Young who placed his eye under water, replaced the corneal refraction by a convex lens, and then found the amplitude of accommodation unaffected. (2) That the eye elongates in near vision, thus causing the rays from near objects to focus on the retina (similar to the arrangement in the mollusc *Pecten*). This also Thomas Young disproved by placing two iron rings which could be clamped together, one in front of and one behind the eyeball. Having very prominent eyes he could do this if the eye being tested were rotated strongly inwards. The phosphene caused by the pressure of the posterior ring, which extended to the fovea, did not change in appearance during accommodation. He thus found no evidence for an elongation of the eye during accommodation. (3) That the lens during near vision advances towards the cornea (similar to the mechanism in the fish's eye). This view was disproved by Tscherning, who calculated that the lens would have to advance nearly 10 mm. in order to give the full amplitude found for the eye, whereas the anterior chamber of the eye is, as we have seen, approximately only 2.6 mm.

This brings us to the two modern theories, those of Helmholtz and Tscherning. The theory of the former (which is the one most generally accepted) supposes that the lens

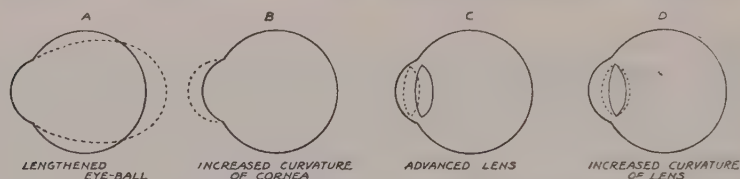


FIG. 227. Methods by which Accommodation of the Refraction of the Eye for Objects at Different Distances could be effected :

- (A.) By lengthening the eyeball. (C.) By moving lens forward.
(B.) By increasing curvature of cornea. (D.) By increasing curvature of lens.

when removed from the eye is strongly convex and is accommodated for near vision. When in the eye, however, it is caused to become flatter through the traction of the zonula of Zinn (suspensory ligaments) on the edges of its capsule, and is therefore focussed for distance. But when the ciliary muscle contracts, it removes the tension on the zonula and therefore allows the lens to return by its elasticity to its more spherical form. Before describing the rival theory it would be well to examine the principal evidence on which Helmholtz' theory has been based. During near vision, measurement by means of the ophthalmometer shows that the anterior surface of the lens advances slightly and becomes at the centre of much greater curvature (10 mm. radius for distant vision, to 6 mm. for near). There can thus be no question that the change in the curvature of the lens is responsible for accommodation. The posterior surface is found to change but little; almost the whole range is therefore produced by the anterior surface. The changes found to occur in the lens of a young adult twenty-five years old may therefore be summarised as follows :—

	Distance.	Near
Radius of anterior surface, in mm.	10	6
Radius of posterior surface, in mm.	6	5.5
Thickness of lens, in mm.	3.6	4
Focus of lens, in mm.	44	30
Focus of lens, in dioptries	23	33
Range of accommodation, in dioptries	10	

If the lens in near vision becomes more spherical owing to the relaxation of the zonula, as Helmholtz supposed, we should expect a lens removed from the eye to be more spherical still, that is, in a state of strong accommodation. Fincham has proved this to be the case. Tscherning stated that the changes in the curvature of the lens are much more complex than those given above. During accommodation not only is there, he says, an increase in the curvature near the centre of the lens, but at the same time a

decrease in the curvature at the periphery. This view he supported by quoting the careful measurements which Young made by means of his optometer, and which have been confirmed by other observers. There is found to be a zone about 1.4 mm. from the centre of the lens where the curvature does not change appreciably. Inside this zone the curvature increases during accommodation, whereas outside the lens becomes flatter.

Tscherning supposed that these changes of curvature are produced by increase in the tension of the zonula during accommodation, in other words exactly the opposite action to that which Helmholtz supposed to occur. This question as to whether tension upon the zonula is associated with near or distant vision can therefore be used as a criterion between the rival theories. Experiments have shown that the chorioid moves forward during accommodation in both man and animals; further Hess has shown that, when full accommodation has been performed, the lens is only loosely supported, so that gravity can act on it and cause it to sink slightly in relationship to the other eye structures. These effects appear to be definitely in favour of Helmholtz' theory, and against that of Tscherning. Additional evidence on this point is provided by the experiments of Hartridge and Yamada (1922). They found the unaccommodated eye of the cat to have a power of about 65 dioptries. They also found that the cornea had a power of about 40 dioptries, while that of the crystalline lens removed from the eyeball was 50 dioptries. From these values the average power of the fully accommodated eye was calculated to be 80 dioptries, that is some 15 dioptries more than that found for the

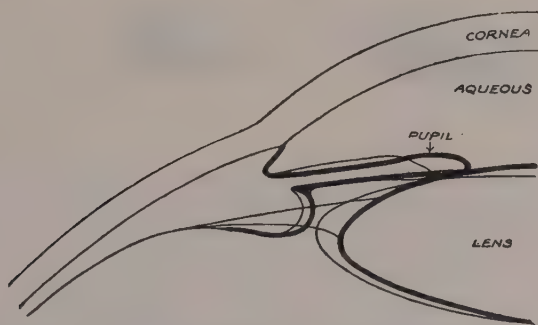


FIG. 228. Diagram to show the Changes in the Position and Shape of the Eye Structures during Accommodation.

Thin line at rest; thick line during accommodation.

intact unaccommodated eye. Now on Helmholtz' theory the cornea and lens would be expected to have a power greater by about 15 dioptries than that of the intact eye when unaccommodated, because in the latter case the lens is being flattened by the traction of the ligament, whereas on Tscherning's theory no such difference would be expected. This evidence is therefore definitely in Helmholtz' favour. The way in which the contraction of the ciliary muscles causes slackening of the zonula, may therefore be given with some degree of confidence in Helmholtz' theory.

THE MECHANISM OF ACCOMMODATION. The ciliary muscle consists of two separate sets of unstriated muscle fibres: the more superficial set of radial or longitudinal fibres, the deeper of bundles of radial fibres. The former take their origin from the sclero-corneal junction, and are attached to the anterior part of the chorioid coat behind the ciliary processes. When these fibres contract, they draw the chorioid forward and inward, the ciliary processes tending to occupy a smaller circle. The circular fibres lie in the substance of the base of the ciliary processes so that, when they contract, they cause the apices of the processes to come together. In addition to these two sets of fibres, a third set has been described as meridional. These are, however, part of the radio-longitudinal set from which there does not appear to be much object in differentiating them. The ciliary muscles therefore have a common action, causing the ciliary processes to form a smaller circle. The zonula of Zinn, or suspensory ligament, is formed of a

large number of very fine fibres which run from the ciliary processes to the capsule of the lens. Further, those which arise posteriorly are attached anteriorly and vice versa. When the ciliary muscle is in a state of rest, the tension in the chorioid set up by the intraocular pressure causes the ciliary processes to be pulled in an outward and backward direction and therefore puts tension on the lens capsule through the zonula. The lens thus tends to be flattened and accommodated for distance. On stimulating the ciliary muscle the tension in the chorioid is opposed and the ciliary processes approximated (Fig. 229). The zonula thus becomes slack, and the tension of the lens capsule decreases, allowing the lens to take up its more natural spherical shape, and thus to focus the rays from nearer objects.

INNERVATION OF MECHANISM OF ACCOMMODATION. The ciliary muscle is innervated through the 3rd nerve, its nucleus being situated near the mid line under those of the pupils. Owing to the close association of the nuclei on the two sides, it is impossible to cause accommodation of the eyes separately. From this nucleus the fibres travel down with the rest of the nerve through the outer wall of the cavernous sinus, and when they reach the orbital cavity are given off to the ciliary (lenticular) ganglion, where they

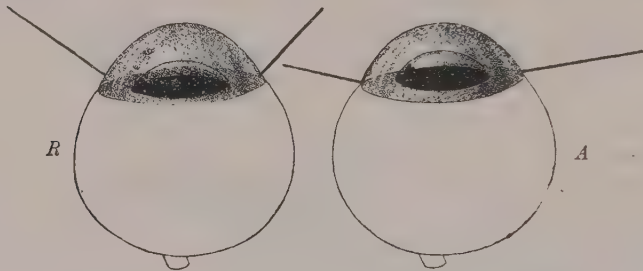


FIG. 229. Accommodation in the Cat's Eye. (BEER.)

R. Distance.

A. For Near Vision.

Two needles have been passed through the edge of cornea into the ciliary bodies, to show forward movement of the latter during accommodation.

anastomose with nerve cells, the processes of which then proceed through the short ciliary nerves to the eyeball.

The position of the higher centres connected with the nuclei concerned in accommodation is not definitely known; it is believed to be in the occipital cortex. But since it is possible to carry out willed changes of focus as well as subconscious ones, there must be connections with other parts of the brain as well.

THE AMPLITUDE OF ACCOMMODATION in the emmetropic (normal) eye is measured by ascertaining the nearest point from the eye at which perfect vision can be obtained. Since it is possible that the eyes, when examined separately, can focus nearer objects than they can when used together (owing to the limitation in the power of convergence), one of the eyes should be closed when making the determination. In the ametropic (abnormal) eye it is necessary to determine the far point as well as the near, since the former may not be at infinity as it is in the emmetropic eye. But other difficulties are encountered because, in the case of hypermetropic (long-sighted) eyes, an object placed at infinity still requires some accommodation in order to focus it. Lastly there comes the personal equation of the patient, since it is found that, even when apparently fully relaxed, the instillation of atropine usually causes some further relaxation of the accommodation; so in the same way the instillation of eserine is usually followed by a definite increase in the accommodative effort over that which can be voluntarily exerted. To obtain the maximum amplitude of the accommodation these drugs should therefore be used. Where a comparative and relatively inaccurate value is alone required they may be omitted. Of the many methods that may be employed, probably the simplest is by the use of the set of trial lenses, which vary in their curvature by small uniform amounts from strongly convex (plus) to strongly concave (minus). The test object consists of a pin placed vertically in a board at any fixed distance from the eye, a white surface being arranged behind it. A pair of spectacles to hold the trial

lenses is placed before the eyes, and in them are inserted two metal plates with two vertical slits in them, so that each eye in turn may look at the test object through the slits in the plate opposite it. To determine the *near point*, minus (concave) lenses of gradually increasing power are placed before one of the eyes, the other being closed, until one is found that just causes the image of the pin to appear double. The power of the next weaker lens is therefore taken to be the correct one. To determine the *far point*, plus (convex) lenses of increasing power are tried in a similar manner, and that one taken which just does not cause appreciable doubling. The difference between the power of the two lenses found in this way gives in dioptres the value of the amplitude of the accommodation. Care should be specially taken to see that the value found for the concave lens has the minus sign placed in front of it. Thus if it was found that the far point was reached by the use of a convex lens of 2.25 dioptres, and that the near point required a concave one of 7.5 D., then the amplitude is not 5.25 D. but 9.75 D. Careful measurements made in the above manner show that there is for different ages an average range of accommodation. In youth the amplitude is large, but it decreases uniformly to old age, and this decrease is called *presbyopia* (old-sight). The amplitude found as a rule at different ages is approximately constant and is given in the Table below.

Age in Years.	Accommodation in Dioptres.
10	13.8
15	12.6
20	11.5
25	10.2
30	8.9
35	7.3
40	5.8
45	3.7
50	2.0
55	1.3
60	1.1

This gradual reduction in the amplitude of the accommodation is caused by the hardening of the crystalline lens, which with the advance of years robs it of the elasticity of youth. As a rule the change goes on unheeded till the time comes when the near point of vision has receded so far from the eye that the book has to be held at a distance, in order to be focussed clearly. Then it is found that the print, particularly if it is fine, becomes unreadable, and convex glasses have to be worn. It is at that time that presbyopia may be said to begin, usually at an age of 45 to 50 in emmetropia. In hypermetropia, presbyopia shows itself earlier than normal, and in myopia (short-sight) later. The reason for these differences will be described when dealing with these conditions.

The mechanism of accommodation is affected in a number of pathological conditions; the principal ones will be given. Paralysis of the ciliary muscles frequently occurs after diphtheria and influenza: it is probably due to bacterial toxins circulating in the blood. The paralysis usually disappears during convalescence. Loss of accommodation is frequently one of the first symptoms of glaucoma: in this case the cause is the abnormally high intraocular tension, since that will cause so great an increase in the normal tension of the chorioid that the ciliary muscles have not sufficient power to draw the edges of the chorioid and ciliary bodies into a circle of smaller radius, and thus to allow the lens to accommodate. Apparent diminution of the amplitude of accommodation combined with apparent myopia (short-sight) occurs in patients who have spasm of the ciliary muscles. This is found in two types of cases, children with eye-strain, and women with hysteria. In both, the employment of atropine yields the normal amplitude, and at the same time removes the apparent myopia, thus indicating the cause of the trouble. Occasionally the amplitude of accommodation is different in the two eyes, and is accompanied by unequal pupils. Such a condition may follow an accident or be caused by specific toxins.

THE EFFECT OF DRUGS on the accommodation has already been alluded to. In ophthalmic practice three are used in order to paralyse the ciliary muscle, namely atropine (one-half per cent. solution), homatropine (2 per cent.) and scopolamine (one-fifth per cent.). One of these drugs is placed within the conjunctival sac, and from here it slowly travels, probably by diffusion *viâ* cornea and aqueous, to the ciliary and iris muscles, both of which are paralysed. This fact is of the greatest importance, for if this path did not exist the use of these valuable drugs would hardly be possible. Contraction of the ciliary muscles and of the sphincter pupillæ is caused by the drugs pilocarpine and physostigmine (eserine). One of these is often used to counteract the effects of the atropine group.

6.—THE REFRACTION OF THE EYE

Since the eye forms an image of external objects by means of its refracting media, it is found to have properties and to suffer from defects similar to those met with in the case of other optical systems. We may therefore treat the eye as if it were an optical instrument, and estimate its efficiency from that point of view. In the first place, therefore, we must consider what kind of an image it would form if it were a perfect lens system, suffering from no kind of aberration. Our experience of other lens systems, well-nigh perfect, has shown us that the image of a distant point source of light is not a mathematical point, as geometrical optics would have us believe, but is on the contrary a definite pattern of quite considerable size, the shape and dimensions of which can either be calculated from the conditions, or may be seen, measured and photographed by appropriate means. The formation of this pattern is due not to any defect of the lens, but to the fact that light is a form of wave motion, which exhibits a property called diffraction.

DIFFRACTION OF LIGHT. When a broad wave of light surges through the ether from a distant source of light, its front travels straight and inflexible under the influence of certain well-known laws. These in popular language restrain the tendency of a portion of the wave front to deviate, because of an equal effort of a neighbouring portion of the wave front to do the same thing, only in the opposite direction. At the edges of the wave on the other hand there is no neighbouring portion from which to obtain support, and therefore these edge portions tend to spread sideways more and more from the main wave. A narrow ray of light therefore, after passing through the pupil of an optical system, will show this phenomenon to such a marked extent that only a small portion of the total amount of light will actually reach the goal defined by the original wave front. The smaller the pupil and therefore the narrower the beam of light, the greater the amount of spreading that we should expect to find. And experiment shows that this is the case. Further we should suppose that, in the case of any one beam, the more spreading would occur the further the ray has to travel. This also is found to be the case. Lastly, if waves of different wavelength were tried, we should expect a short wave to suffer more than a long, because to the short wave the distance travelled would seem relatively greater. And so it is. We can therefore summarise the above by saying that the size of the diffraction pattern formed by any lens system varies directly as the focal length of the system and the wavelength of the light, and inversely as the diameter of the pupil through which the light passes. In the case of any lens system such as the eye, in which the pupil is circular, experiment and calculation are agreed that the image of a point source consists of a series of concentric rings of light, having a bright spot at their centre. The diameter of this spot in the case of the eye is found to be 0.01 mm. with a pupil of 2 mm. diameter. No matter how perfect the eye be as an optical instrument, diffraction sets a limit in this way to the perfection of the image that can be formed. This should not, however, be thought of as a defect, but as a property, since it is caused by the nature of light itself. In the consideration of the principal optical errors of the normal eye, we have to decide in each case, not only to what extent the defect is present, but whether the defect produces any noticeable change in the diffraction pattern which may affect definition.

DEPTH OF FOCUS, like diffraction, is a property of a lens system and not an aberration. Its origin may be explained as follows :—Suppose objects 100 metres away to be forming sharp images on the retina, then objects at 200 metres will form images which come to a focus slightly in front of the retina, and objects at 50 metres images that are slightly

behind. If however the focussed points are only a short distance in front of or behind the retina, the image of a distant point which fell on a single cone would still do so although its distance from the eye had been altered, because the cone has a certain diameter. Depth of focus in the case of the eye is the greatest distance through which a point can be moved and still produce an image which falls exactly on a cone without spreading at all on to neighbouring ones. For example, in the above case the distance moved was from 200 to 50 metres, that is, the depth of focus was 150 metres. Now it is found in the case of any lens system that depth varies with the aperture of the pupil. Thus in the case of the eye the following values are obtained :—

Pupil diameter.	Depth at infinity.	Depth at 25 cms.
1 mm.	From inf. to 8 metres	3.2 cm.
2 " "	" " 16 "	1.6 "
3 " "	" " 24 "	1.1 "
4 " "	" " 32 "	0.8 "

We see, therefore, that not only does depth decrease as the aperture of the pupil increases, but that it also decreases as the mean distance of the objects from the eye decreases. Thus with a pupil of 3 mm. the eye, if focussed sharply on objects 24 metres away, would also be in focus for objects at infinity and also for objects at 12 metres. Depth of focus is therefore considerable at this distance. But if the eye is working at the ordinary reading distance (25 cm.) depth would be 1.1 cm. only. At a pupil diameter of 1 mm., depth would be increased threefold, and therefore the closure of the pupil, which accompanies accommodation and convergence for near objects, has the valuable property of increasing the depth of focus at the same time.

CHROMATIC ABERRATION OF THE EYE. We have seen that white light consists of a number of rays of different wavelength, and that on refraction the short rays are more bent than the long. When, therefore, white light is incident on a lens, the rays of short wavelength come to a focus in front of those of longer wavelength. This difference of focus for rays of different colour is called chromatic difference of focus. Experiment shows that, when such a series of foci are formed by the eye, the accommodation is so adjusted that the rays of greatest intensity (usually yellow rays) form the most sharply focussed image, and the colours of longer and shorter focus form blurred discs of light of relatively low intensity on top of this. Under these conditions it is found that quite well defined images are produced. Thus, with a pupil of 2 mm. diameter, approximately 70 per cent. of the light falls in an area of 0.005 mm. diameter. Further it may be shown that a lens system such as the eye, which suffers from chromatic aberration, produces an image that is only just appreciably worse than one that is perfectly corrected, when the effects of diffraction are taken into account in both cases. But since the effects of chromatic aberration increase as the pupil enlarges, while those caused by diffraction decrease, it is clear that the larger the pupil the more does chromatic aberration tend to spoil definition. But as this is accompanied by decrease in diffraction, the two changes taken together have the effect of leaving the actual definition practically unchanged. This important conclusion will be referred to again more fully in the last section. Beside effects on definition, chromatic aberration causes small bright points of light on a dark ground to form images which are largely composed of yellow rays, and on the other hand small black objects on a bright ground to be purple in colour. The reason for these colours being unnoticed in ordinary circumstances is due to the recognition by the eye of the presence of the complementary colour which forms a fringe round the central point.

SPHERICAL ABERRATION OF THE EYE. The employment of spherical surfaces to bound optical media leads to a difference in the position of the foci of rays that have passed through the centre of the lens and those that have passed through the more peripheral parts. The latter usually form a focus nearer to the lens. Since the eye is bounded by nearly spherical curves, it has been assumed that this aberration must be present in this organ.

It should be remembered, however, that the crystalline lens has a structure quite different from that found in the lens systems of optical instruments. For the presence of a graduation of optical density, culminating in a nucleus of relatively great curvature, causes rays passing through the centre of the eye to be refracted to a greater extent than more peripheral rays, or in other words exactly the opposite effect to that produced by spherical aberration. Measurements on the eyes of different individuals, therefore, show the presence both of small amounts of under-correction (when the correcting effect of the lens nucleus has not been enough) and also actually of over-correction (when the lens nucleus has had too big an effect). In quite a number of cases the amount of spherical aberration is negligible even with pupils of 4 mm. diameter. With larger pupils there is probably a certain amount of under-correction, but this again is less than would be found in the case of spherical surfaces, because the more peripheral parts of the cornea are flattened and therefore refract less (as Gullstrand has shown). We may say, therefore, that in everyday life the effects of spherical aberration are altogether negligible, compared with those of diffraction and chromatic aberration.

PERIPHERAL ABERRATIONS OF THE EYE. So far the definition of an image lying on the principal axis of the lens has alone been considered. When this is not the case, other conditions are encountered which are more unfavourable in their effects. In the first place, the rays that form images on the peripheral parts of the retina make considerable angles with the surfaces of the eye media. This will cause chromatic difference of magnification, since blue rays will be more bent and will therefore form smaller images than red rays. It will also introduce 'comma,' that is, the effect due to disobedience of the sine condition. It is seen at once, therefore, that the image formation by the periphery of the eye is altogether more imperfect than it is at the centre. The presence of the nucleus of the lens still further impairs the marginal definition. In fact we may say that in the eye, as in the microscope objective, the marginal images have been sacrificed in order thereby to improve the central ones. That this has been a very valuable result will be shown later. It will be shown in the next section that the most sensitive region of the retina is not exactly in correspondence with the optical axis of the lens system of the eye, being displaced approximately 0.5 mm. to the temporal side. We must therefore consider briefly to what extent the peripheral aberrations of which we have just spoken will interfere with the definition.

THE SINE CONDITION (COMMA). This aberration is found to show itself in optical instruments by a difference in the position of the various parts of the image produced by the separate zones of the lens. Instead of rays from a point source coming to a focus at one and the same point, they are found to form a fine line or comma, the tail of which points towards the optical axis. If the optical system obeys a rule called the sine condition, comma is corrected. The eye appears to obey this condition exactly, and therefore, so far as comma is concerned, the displacement of the fovea to one side of the optical axis is no disadvantage.

CHROMATIC DIFFERENCE OF MAGNIFICATION, like chromatic difference of focus, is caused by the unequal refraction of light rays of different wavelength. But since, on refraction, violet rays are more bent than red rays, their foci form not only at different distances from the cornea, but also at different angles with the optical axis. It follows from this that objects, subtending a considerable angle at the eye, produce images which are smaller for violet rays than they are for yellow rays, while those for red rays are larger still. Images produced by rays of different wavelength therefore vary in size. Since that part of the retina which possesses the best vision (the fovea) is situated to one side of the optical axis, all images formed on it must suffer from this error. Far from this being a disadvantage, however, it is surprising to find that there is on this account an actual diminution of the effects of chromatic aberration, and that the displacement is therefore a wholly beneficial one. That this is probably the explanation

of the development of the most sensitive part of the retina at this point hardly requires indication.

RADIAL ASTIGMATISM must, according to optical theory, be present in the image formed on the fovea. Experiment shows, however, that its effects can be to a considerable extent neutralised by positive axial astigmatism such as is found in the eye of emmetropes. The presence of this aberration may therefore be ignored so far as the fovea is concerned.

STRUCTURE OF FOVEAL IMAGE may be determined approximately by considering in turn the effects of different aberrations on the light rays which enter the eye. For this purpose the only errors of importance are chromatic differences of focus and magnification. In addition, however, we must take into account the very important effects of diffraction. The final results of such a calculation show that the images of rays of different wavelength overlap one another. At the centre of the image is seen the sharp yellow focus of the highest intensity. Eccentric to it, and overlapping one another are seen the diffuse red and green foci, which are of much less intensity. Where these overlap they produce a compound yellow according to the rules of colour mixture. Further outwards is the still more diffuse image of the blue rays, which is of almost negligible intensity. It is seen therefore that the centre of the image is entirely occupied by the sharp and intense focus of the yellow rays. Not only are these rays the brightest in the spectrum, but they are also those nearest to white light in their physiological properties. It is because of this structure of the image that the acuity of vision is so great at the fovea.

PERIPHERAL IMAGES have, as stated above, been to a considerable extent sacrificed, so far as their definition is concerned, in order to obtain the best possible conditions at the fovea. We find, therefore, at the periphery images that in no way compare with those formed near the optical axis of the eye. Even here, however, there is evidence that the eye has been designed to give the best results obtainable. The two aberrations which most concern us other than those already mentioned, are curvature of the field and distortion.

CURVATURE OF THE FIELD is found in all positive lens systems of simple formula. Since the photographic plate is flat, it is one of the principal errors to be corrected in the photographic lens. In the eye, on the contrary, the effects of the aberration have been avoided, not by correcting the lens system, but by curving the sensitive surface to correspond. Calculation shows that, for correction, the radius of the surface of the retina should be somewhat shorter than the equivalent focal length of the lens system. But we know that the radius of the retina is approximately 10 mm., while the focal length of the eye is 15.5 mm. The theoretical conditions therefore appear to have been fulfilled.

DISTORTION shows itself in photography by a curving of lines which are known by experience to be straight. But this straightening, which can be readily effected by suitably designing the lens system and by using a flat plate, is found to be accompanied by a change in the size of an image, according as it is formed at the centre or the edge of the plate. But such a change in size would be most disadvantageous in the case of the eye, because not only would the apparent size of objects vary, according as their images fell on the centre or the periphery of the retina, but also the perception of perspective, which, as we shall see later, depends on the correct estimation of the differences between the position of near and distant objects, would be seriously interfered with. In the eye it is very much more important that images should keep the same size, than that distortion should be corrected by optical means. In order that images shall be constant in size, the retina must be curved to approximately the same extent as is required for the correction of curvature of field. We see, therefore, that the shape of the retina has a very important effect on peripheral vision, and further, that so far as we are able to judge, the best shape has been evolved.

OTHER OPTICAL DEFECTS. The analogy between the eye and the photographic camera shows that there are a number of other defects from which the eye may suffer. These are (1) the presence within the eyeball of light scattered from one part of the retina to another (equivalent to shiny bellows in the camera); (2) the spreading of the image formed on one part of the retina to neighbouring portions (equivalent to halation); (3) the illumination of the retina by light internally reflected at the different optical surfaces (known in photography as flare); (4) the exposure of parts of the retina close to those receiving the image, because of imperfection in the optical system (called irradiation).

Scattered Light. In describing the histology of the retina it will be shown how generously the layer of cells lying immediately outside the sensitive layer of rods and cones is supplied with pigment; the object of this is clearly to absorb scattered light. In spite of this, however, we find considerable amounts of light being reflected back

again by the retina; in fact it is this light that enables us to see the retinal nerves and vessels through the ophthalmoscope (see page 427). The spherical shape of the eyeball will cause the greater part of this reflected light to travel towards the front of the eye, and to fall on an insensitive layer of iris or retina anterior to the ora serrata. From here it will be reflected again on to the retina, but with such reduced intensity as not to cause stimulation. Light reaching the anterior part of the retina through the pupil would, after reflection, tend to travel towards the posterior part of the retina, which is the part most sensitive to light. The intensity of these peripheral rays is, however, diminished in a number of ways: firstly, by the eyebrows, cheeks and nose; secondly, by the eye-lashes when the lids are approximated, as they are when looking towards a bright light; thirdly, by the relative smallness of the pupil for oblique rays (the pupil being a slit-shaped instead of a circular opening for such rays). The effect of scattered light in the eye is therefore eliminated in this way. It should be noted that in certain animals, which have very acute night vision, the pigment cells of the chorioid at the posterior pole of the eye are iridescent, and form a highly reflecting surface behind the retina, which is called the tapetum. The object of this would seem to be to increase the stimulus of a given intensity of light, but the presence of this reflecting layer must increase the amount of scattered light in the eye, and would therefore appear to be of disadvantage in day vision.

Halation. This is caused in the camera by the image that has formed on the plate being reflected back again on to the plate from the internal surface of the glass. This is not apparent in the photographic film, because owing to the thinness of the gelatin film the reflected image falls back on to the same part of the plate again. In the case of the retina the reflecting layer must be exceedingly close to the sensitive layer, if indeed the two are not identical. Halation in the eye would therefore appear to be negligible in amount.

Flare. The amount of light reflected by the surface bounding two optical media increases as the difference between their refractive indices increases, and also with the angle which the light makes with the surface. Therefore, other things being equal, the smaller the angle of incidence and the more nearly the refractive indices are identical, the less the amount of flare will be. In the eye, the lens system is, as it were, immersed in a medium of almost the same refractive index as itself; and further, even that difference is reduced by the fact that the actual refractive index of the crystalline lens is, owing to its peculiar structure, very much less than its equivalent R.I. Flare in the eye must therefore be quite inconsiderable in amount.

Irradiation. That this phenomenon is present in the eye may be shown directly by experiment. If, for example, an electric light filament be looked at before and after the switching on of the current, the increase in thickness on illumination is obvious. Its cause appears to be imperfect definition, spreading of the light from one retinal element to its neighbours, or spreading of the effect of the nerve impulse, either at the retina or even in the brain itself.

ABNORMAL REFRACTION OF THE EYE

It would almost be anticipated that such a complicated organ as the eye would be found to show individual abnormalities. A further consideration would probably suggest to us that, considering the smallness of the change that is necessary in any one of the optical media in order completely to destroy definition, it is nothing short of astonishing that abnormality of refraction is relatively so uncommon. In the newly-born the eye is almost always long-sighted (hypermetropic); this is due to the eyeball being too small for the optical system which it contains; the image formed by the latter is therefore focussed behind the retina. As age advances the eyeball grows until the point is reached at which the eye is emmetropic (normal). If, however, the child is allowed to use its eyes too much for near work, the eyeball goes on increasing in size until it has overshot the mark, and has thus caused the eye to become short-sighted (myopic). There would appear to be some kind of automatic control, which causes the eye to grow till it is in adjustment with the conditions most frequently encountered. This hypothesis is confirmed by the fact that if a child which is beginning to develop short-sight is prevented from using near vision for a year or two, the

development of short-sight stops. The importance of the early detection of the onset of short-sight therefore cannot be too strongly urged.

THE METHODS OF DIAGNOSIS. The detection of errors of refraction in the eye may be effected in various ways, each of which is said to possess advantage. Some of these have come into such general use that they may be briefly considered as an introduction to the description of the more important types of error which they are used to investigate.

THE DETERMINATION OF THE VISUAL ACUITY. It has been found by experiment that persons with normal sight can distinguish between objects when the angle separating them is not much less than one minute. Test type has therefore been prepared in which the letters are composed of lines which subtend this angle at the eye, when the type is placed at a standard distance of six metres. Persons who are able to read the type at this distance are said to have normal vision. Above these standard letters are placed a series of larger letters, which at two, three or four times the standard distance would subtend the standard angle. A person with reduced acuity might be able to read at six metres the type that should be read at sixty. He therefore has vision which is one-tenth the normal. Such a person might have long-sight, short-sight or astigmatism: to determine which is present, there is placed before his eyes a lens-frame, into which can be inserted any two of a large selection of glasses of different power, which are known as trial lenses. These are tried in turn in an orderly manner, until some are found which allow the man to read the standard type at the standard distance. His visual acuity is now at the normal and the strength and shape of the glasses in front of his eyes is carefully noted, so that others of the same power may be fitted to spectacles for him to wear. If the glasses are found to be convex (plus), then he was suffering from long-sight (hypermetropia), and if concave (minus) from short-sight (myopia). Very great care must be taken in this latter case, however, not to prescribe a stronger lens than is necessary. But if, on the other hand, cylindrical lenses had to be used, then he had astigmatism, either alone or in conjunction with long- or short-sight.

THE METHOD OF RETINOSCOPY. Such a method as that just described could only succeed if the person tested were an intelligent adult, because we depend entirely on his giving the correct answer, when we ask if the substitution of a different lens for the one we have already placed before him makes vision better or worse. With a child such a method could never succeed. Another method is therefore practised, which has the great advantage of being independent of the patient; in fact for the purpose of the test he might be blind. This method consists in throwing, into each of his eyes in turn, a beam of light reflected from a plane mirror, in the centre of which is a hole through which the observer looks. When the beam of light is directed into the patient's eye, the observer sees through the pupil a pink reflected beam of light. As the mirror is gently tilted, so as to throw the beam slightly upwards and slightly downwards, so the pink beam appears to move up and down behind the patient's pupil. If it moves down as the mirror is tilted down, the movement is said to be *WITH* the mirror, and the patient is hypermetropic, requiring plus spectacles. If on the other hand the beam moves '*AGAINST* the mirror,' minus spectacles are required, since the patient is short-sighted. By placing glasses of different power in front of his eye, until one is found which causes the pink beam to move neither with nor against the mirror, the actual power for the spectacles required by the patient is ascertained. It should be carefully noted however that, since the observer is standing at about a metre distance from the eyes of his patient, plus one D must be subtracted from the power of any glasses that are found to be necessary. Thus if the patient was found to be myopic and minus 7 D spherical lenses were required to neutralise the movement of the beam, then the power that should be ordered is minus 8 D spherical. This test is found to work admirably in practice. It is usual to paralyse the pupil reflex and the accommodation of the patient previous to the test by the use of atropine, but some say that this is unnecessary.

OTHER METHODS. Of other methods of testing vision little need be said: some require the use of special instruments such as the optometer and the refractometer. Another again depends on the determination of both the far and near points. This is of distinct value because it at once gives the amplitude of the accommodation, which is an important determination. Others are based on the use of the ophthalmoscope. But none of these methods is so simple or accurate as the method of retinoscopy described above.

STENOPEIC APERTURE. Often in practice the question arises as to whether low visual acuity is due to defect in the optical media of the eye, or to disease of the retina. This question can be readily answered by placing in front of each eye in turn a metal disc in which has been drilled a hole 0.3 mm. in diameter. If this improves acuity

the defect is not in the retina ; if it does not, it is. This test should be done in a good light because of the small amount of light passed by the hole. A hole used in this way is called a stenopæic aperture.

HYPERMETROPIA OR LONG-SIGHT. There are two principal varieties of long-sight ; firstly, that in which the eyeball is too small and too short for the normal optical system ; secondly, that in which the eyeball is normal but the refracting power of the lens below the normal. The first variety is found in childhood, because the optical system reaches its adult size much earlier than does the eyeball. In the majority of children the eyeball continues to grow until it is the correct size, and therefore long-sight disappears. In a certain number of cases this does not happen, and therefore long-sight remains through life. The second variety is found in old age, and appears to be due to the absorption of water by the lens. The result in both cases is that the rays of light from distant objects are brought to a focus behind the retina, and therefore in order to focus them the accommodation has to be used (see Fig. 230). It follows from this that there is less accommodation remaining for the focussing of near objects, and therefore an inability to see distinctly at relatively short distances from the eye. Thus the use of the term long-sight.

Hypermetropia in adults is, therefore, more an abnormality than a disease ; it causes a disposition, however, to three more serious conditions, namely glaucoma, internal

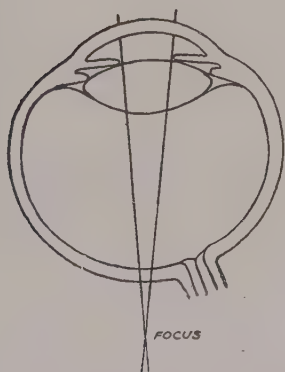


FIG. 230. Hypermetropic Eye.
The eyeball is too short and therefore rays from a distant object come to a focus beyond the retina.

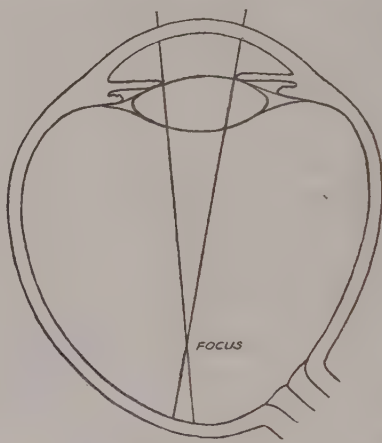


FIG. 231. Myopic Eye.
The eyeball is too long and therefore rays from a distant object come to a focus in front of the retina.

strabismus and eye-strain. Glaucoma has already been described (see p. 398) ; it is due to an abnormal rise in the intraocular pressure, which occurs owing to the free escape of the aqueous humour at the filtration angle being checked. Now in hypermetropia we have seen that the eyeball is too small for its optical apparatus, and therefore the lens occupies too much of the space in the small anterior and posterior chambers. This causes the ciliary bodies and roots of the iris to be squeezed and greatly reduces the space at the filtration angle. An attack of glaucoma is therefore more liable to occur in the hypermetrope than in a person with normal refraction.

Internal strabismus is caused in hypermetropia by the accommodative effort that is made in order to focus an image on the retina because, as we have seen above (p. 390), convergence and accommodation are associated actions. When, therefore, the long sight has been corrected by means of spectacles, and the accommodation is no longer called into play for seeing at a distance, the associated convergence no longer occurs and the strabismus disappears.

Eye-strain is caused in hypermetropia by the continual call for accommodation. Further this must occur without convergence, for otherwise diplopia (seeing double) and strabismus develop as just described. A special strain is therefore placed not only on the ciliary muscles, but also on the external eye muscles. This state of affairs very rapidly causes fatigue, and headaches are therefore common.

The treatment of long-sight consists in prescribing suitable convex spectacles. It should be noted that the amount of long-sight actually present is shown only when the accommodation has been paralysed by atropine, because the patient has grown so

accustomed to use his accommodation in ordinary vision that he is unable voluntarily to relax it. There is a certain amount of spasm of the accommodation. Because of this, the glasses prescribed should be less strong at first than the full correction shown to be necessary. These may be substituted by more powerful ones later.

MYOPIA OR SHORT-SIGHT. In this condition parallel rays, that is those coming from distant objects, come to a focus so far in front of the retina that the image appears blurred (see Fig. 231). Myopia may be caused in two ways, which are similar but opposite in action to those that cause hypermetropia; the first type is caused by the eyeball being too long, and the second by the refraction of the lens being too high. The former, which is the more common, usually develops in youth, particularly at the school age when the growth of the body makes special demands on the system, and at the same time feeding is usually bad. The constant use of the eyes for near work causes them considerable strain, which they are unable to withstand owing to their being unable to compete for nourishment with the rest of the body. The chorioid and sclera therefore become thin, are no longer able to stand the tension set up by the intra-ocular pressure, and therefore expand, causing the eyeball to become larger than normal, and taking the retina beyond the focus of the optical system. The treatment of myopia is therefore not only the wearing of spectacles, but the absolute prohibition of near work or close study, the administration of extra-nourishing food and an open-air life for a year or more. If these steps are taken at once, the myopia may get no worse, and may in fact get better. But if neglected the condition will almost certainly get worse. As myopia is a disease particularly liable to occur at the school age, schoolmasters and others associating with children should be on the look out for conditions likely to cause it, such as bad light, bad food and poor ventilation, and for its presence in any of the children. Glasses should always be prescribed, and care taken that the child wears them constantly, because it is found that beside assisting good definition and relieving eye-strain, they actually tend to check the further development of the trouble.

Certain complications sometimes attend myopia; these are divergent strabismus, eye-strain, and spasm of the accommodation.

The divergent strabismus has a similar origin to the convergent strabismus met with in hypermetropia, namely association of deviation of the eye axes with the adjustment of the accommodation. Now since, in the normal individual, the relaxation of the accommodation of the eye is associated with parallel axes of the eyes (in order to look at distant objects), in myopia the disuse of the accommodation for near vision causes the eye axes to remain straight and therefore produces the effects of an external strabismus. The use of glasses introduces again the necessity of accommodation, exactly as if the eye were normal, and therefore abolishes the strabismus. In the majority of cases an actual strabismus does not develop, but there is nevertheless a strong tendency to diplopia, especially when the eyes are tired. The eye-strain which frequently accompanies myopia probably has its origin in the effort to converge the eye axes without at the same time calling the accommodation into play.

Spasm of accommodation frequently accompanies myopia, and has the effect of making the myopia seem greater than it actually is. The true state of affairs is at once found when atropine is used, because the accommodation is thus abolished. Sometimes in children spasm of accommodation occurs without any actual abnormality of refraction. Such cases should be treated with the same care as those that are already developing myopia.

ASTIGMATISM. The condition of the eye called astigmatism is one in which parallel rays are not brought to a focus in a single plane, but in a number of different planes. There are two different varieties of astigmatism. In the first, or irregular, variety

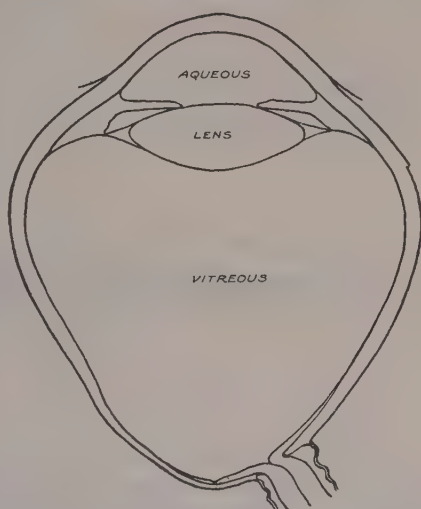


FIG. 232. The Asymmetry of the Eyeball and Kinking of the Optic Nerve caused by High Myopia.

the separate parts of one meridian of the eye form different foci. This is found to occur during the development of cataract in the crystalline lens, and also after ulceration of the cornea. The effects of this form of astigmatism on vision vary with the severity of the condition; in moderate cases a frequent phenomenon is the formation of a double image in the affected eye. Glasses as a rule do not give benefit. In severe types the use of a stenopæic aperture may improve definition.

In the second variety, or regular astigmatism, the parts of any one meridian give the same focus, but the different meridians have different foci (Fig. 233). There are, however, two meridians at right angles to one another, one of which has the longest and the other the shortest focus, the meridians in between showing an orderly sequence between these two extreme values. Thus the use of the term "regular astigmatism." Two types of patient are found to suffer from this condition, those who have inherited and those who have acquired it as a sequence to injury, operation or disease. The effects on vision are varied, but the characteristic features are distortion of objects looked at, and indistinctness of lines in one direction, while those at right angles are quite sharp. Headaches, eye-strain and dimness of vision are very common. Many types are met with because the maximum and minimum meridians may occupy any angle, so long as they are at right angles to one another, and there may be any degree of myopia or hypermetropia.

The diagnosis and measurement of astigmatism present no difficulties. Its existence may be readily proved by causing the patient to look at a figure consisting of a series of lines radiating from a common centre. It is then found that while some of the lines are sharp those at right angles are indistinct. This test also shows the axes of the principal meridians. By retinoscopy (see p. 413) the axes and the amounts of the abnormality in those axes may be readily determined. The treatment consists

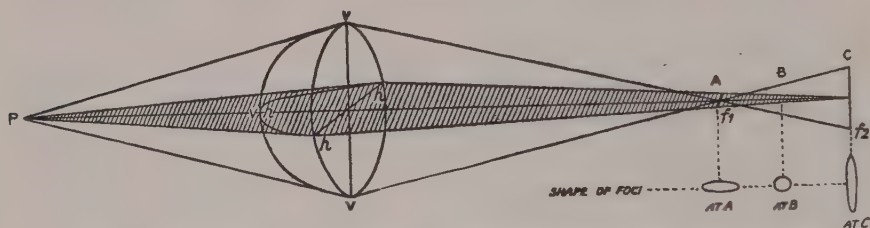


FIG. 233. Showing the Shape of Foci at different Positions in cases of Astigmatism.

in giving spectacles which have been ground on one side to a cylindrical surface. The axis of this cylinder is adjusted to correspond with one of the principal meridians of the eye of the patient. The curve given to the cylinder is that which will cause the focus of the meridian with which it corresponds to be equal to the focus of the other meridian. The other side of the spectacle lens is ground to that spherical surface which will make the eye emmetropic after it has been corrected by the cylinder.

ANISOMETROPIA. The last abnormality of refraction which we have to consider is called anisometropia. It simply means difference between the refraction of the two eyes. The effect on vision is very slight, since it is found that as a rule one eye does all the work, and the image of the other, which is necessarily indistinct, is prevented from reaching consciousness. The result in course of time is that the unused eye loses to a considerable extent its power of seeing and as a result strabismus develops. Treatment consists in giving glasses which correct each eye separately, and then instituting exercises for the poorer eye, in order to improve its vision. The results of this treatment are good.

7.—THE RETINA

The retina is a delicate membrane lying inside the chorioid coat of the eye. Its internal surface lies in contact with the hyaloid membrane of the vitreous body. It is thus supported on both sides. The retina itself consists of two layers, the outer or pigmented, and the inner or nervous. Whereas embryologically the retina covers the whole internal surface of the eye including the ciliary processes and the iris, this is not the case with the nervous layer, because this stops near the equator of the eye at the *ora serrata*, and is here replaced by a layer of columnar epithelium. Opposite the pupil a yellow spot is seen on the retina, the *macula lutea*, and in the centre of this there is an oval depression, the *fovea centralis*. The optic nerve enters the eyeball through an aperture in the sclera and chorioid, and then passes through the posterior surface of the

retina to spread out over the internal surface. In the fovea, however, this is not the case, for the depression at this point is caused by the absence of nerve fibres. The point at which the optic nerve enters the eye is easily recognised from inside the eyeball because the numerous white nerve fibres, as they bend over the edge of the aperture in the retina, form a characteristic white mound called the colliculus, at the centre of which is a depressed portion called the optic cup. It is in the centre of this cup that the central artery of the retina and the corresponding vein first make their appearance. These have the important function of nourishing the retina; the additional blood supply through the intimate contact between the retina and the vascular choroid, although

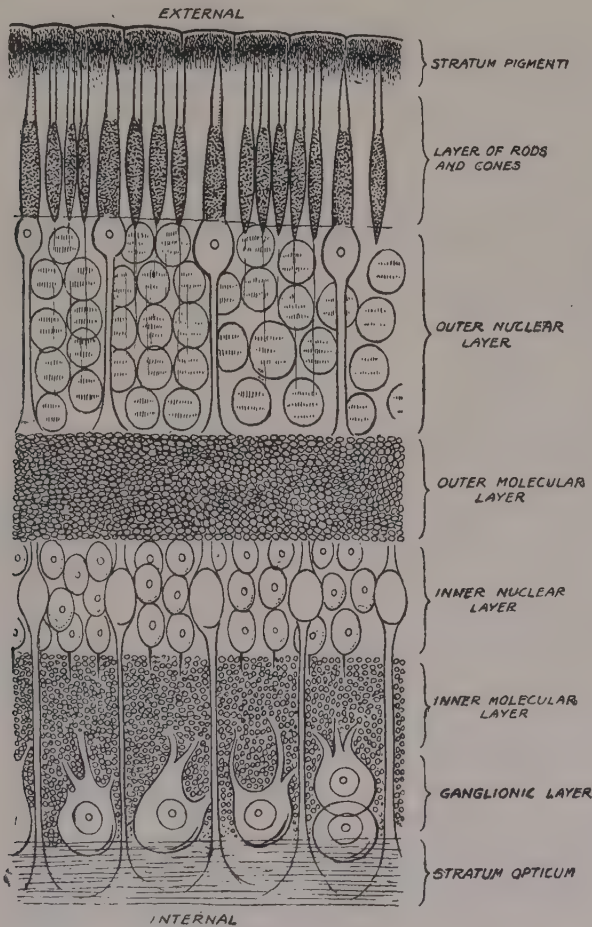


FIG. 234. Diagram of Transverse Section of Retina.

important, is quite insufficient to supply the needs of vision, as is shown by the immediate and permanent blindness which follows blocking of the central artery of the retina.

When sections of the retina are examined under the microscope it is found that they consist of the following layers from within outwards (Figs. 234 & 235) :—

- | | |
|--|---|
| 1. Layer of pigmented epithelium | Developed from posterior layer |
| 2. Layer of rods and cones (bacillary layer) | |
| 3. Outer nuclear or granular layer | Developed from anterior layer of optic vesicle, |
| 4. Outer molecular or plexiform layer | |
| 5. Inner nuclear or granular layer | |
| 6. Inner molecular or plexiform layer | |
| 7. Layer of ganglion nerve cells | |
| 8. Layer of nerve fibres and vessels | |

In order to understand the structure of these layers, it is necessary to keep in mind the fact that the optic nerve and cup are outgrowths of part of the brain. We must therefore be prepared to find in the retina all those structures which are found in every sensory path to intervene between the sense cell and the brain nucleus. In every case the stimulus is conveyed through three sets of neurones or relays before it reaches the brain.

The *Stratum Pigmenti* is the only one that is developed from the external layer of the embryonic optic cup. The epithelium consists of a single layer of hexagonal nucleated cells containing numerous pigment granules. The cells send fine processes between the limbs of the rods. The bases of these cells are firmly attached to the chorioid, and thus give support to the rest of the retina.

The object of these cell processes and the pigment granules which they contain would appear to be either the prevention of an image formed on one part of the retina from spreading to the sensitive elements of surrounding portions, or else the protection of these elements from excessive light action. But it has been definitely proved that the cells themselves have another and important function to perform, namely the

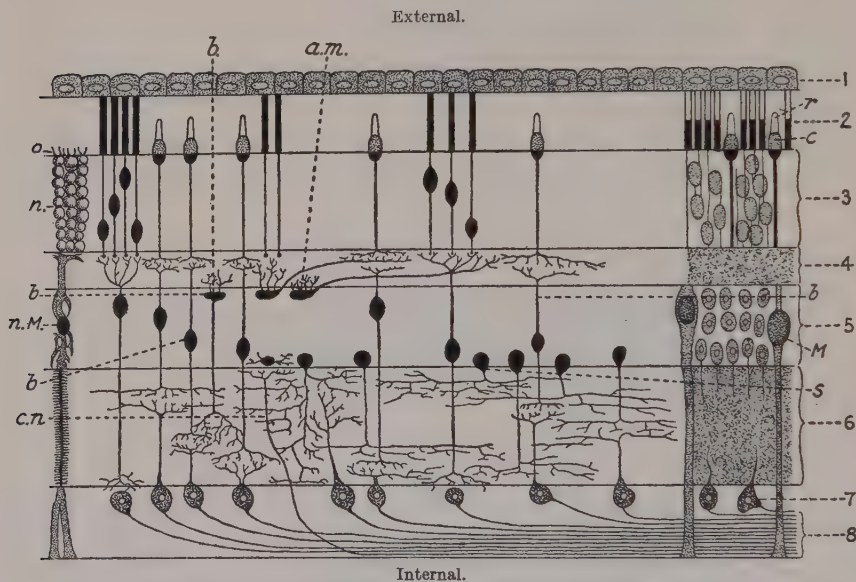


FIG. 235. Diagram to show the different Cellular Structures found in the Retina.

secretion of the pigment called visual purple (rhodopsin). The important functions of this pigment will be described later.

The *Bacillary Layer* of rods and cones is separated from the previous layer by the external limiting membrane. Each rod and cone consists of an outer and inner limb, the forms of which are well shown in Fig. 236. It will be seen that the outer limbs are striated, the cones coarsely, the rods finely; they tend after hardening to break up into discs. The inner limbs of both rods and cones have a strong affinity for dyes.

The *Outer Nuclear Layer* consists of the cells of the first order neurones or the granules of the rods and cones. The cells are nucleated, somewhat smaller than the bipolar cells, and their nuclei are striated. They give off two processes, one of which forms dendrites in the fourth layer, the other connects with either a rod or cone as the case may be.

The *Outer Molecular Layer* is much like the inner; it consists of the dendrites of the second order neurones and the first.

The *Inner Nuclear Layer* largely consists of bipolar second order neurone cells. There are however also present the nuclei of the horizontal cells, and also the nuclei of similar cells, (amacrine cells *a.m.*, Fig. 235) whose dendrites travel in the outer molecular layer. The bipolar cells, which are fusiform in shape and nucleated, are of three kinds: (a) those which connect with rods, (b) those which connect with cones, and (c) giant bipolars which connect with either.

The *Inner Molecular Layer* consists of a feltwork made up by the interlacing dendrites

of the ganglion cells with those of the inner nuclear cells or second order neurones. There are also the dendrites of horizontal cells or spongioblasts (s, Fig. 235). These possibly serve to associate the impulses from different parts of the retina, such as is supposed to occur in the brain. It should be noted that they appear to be absent from the fovea and macula.

The *Ganglion Cell Layer* consists of a single layer of large oval cells. These are nucleated and give off the axons which we have already described, and a bunch of dendrites which ramify with others in the inner molecular layer. Only at the macula is more than one layer of ganglion cells present; this is due to their almost complete absence at the fovea. The macula therefore not only has its own relays but those of the fovea as well.

The *Nerve Fibre Layer* (stratum opticum) consists of the non-medullated axons of the large ganglion cells found in the second layer. These axons are the third order neurones which become myelinated after they have passed out of the eyeball, and travel by paths to the calcarine cortex described on p. 294. Beside the fibres conveying visual impressions there are others which belong to the pupillomotor reflex. Others again bring impulses from the brain to the retina; their functions will be considered below.

It should be noted that beside the structures described above, which have the functional activities of the retina to perform, there are a number of connective tissue elements which form the retina into one coherent structure. Since the retina is developed from an outgrowth of the brain, these structures are similar in type to those met there; we therefore find neuroglia and also long cells which extend through the first seven layers and hold them together, namely the fibres of Müller.

THE DIFFERENT PARTS OF THE RETINA show marked variation in detail. At the fovea (Fig. 237) cones alone are found; only one of these connects to each axon. The structural peculiarities of the fovea may be summarised as follows:—(1) Absence of rods. (2) The cones are longer, more highly developed, and some say more rod-like than those found elsewhere. They are very closely packed, so that their inner limbs are seen in transverse section to have a hexagonal shape, the flat surfaces being in contact with those of their neighbours. (3) The rows of nerve cells and dendrites, which in the rest of the retina lie approximately in line with the rod or cone to which they belong, are in the fovea pressed to one side in a direction away from the centre. In this way a cone may have the nerve cells to which it is connected placed at a considerable distance away in the surrounding macula. It is this displacement of the nerve fibres and their cells that causes the fovea to appear hollow. The purpose of this physiological arrangement would without question appear to be the avoidance, at this important region of the retina, of the scattering of the image which passage through the nerve cell layers would introduce. (4) The fovea unlike the rest of the retina is devoid of blood vessels. The purpose of this arrangement would appear to be similar to that just described. (5) Visual purple is said to be absent from the fovea. This would appear to be connected with the absence of rods.

Round the fovea is a ring in which rods and cones are present in almost equal number. In still more peripheral regions cones are relatively few, and several rods connect with each axon; this reduces the relative number of nerve fibres.

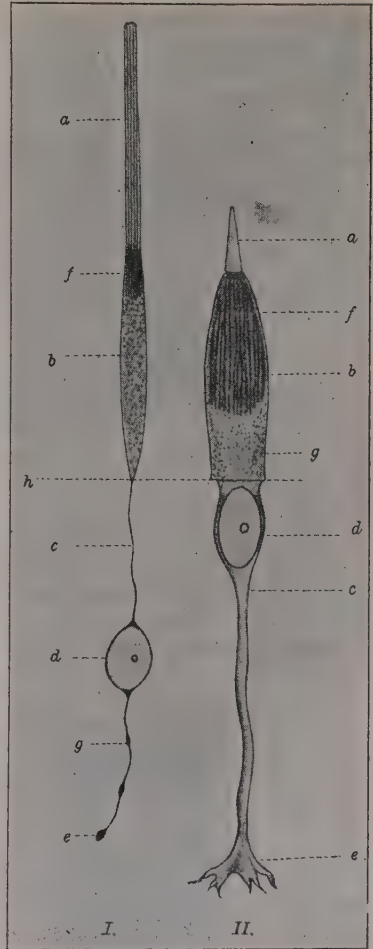


FIG. 236. (R. GREEFF.)

I. A Rod.

II. A Cone of Mammalian Retina.

h. External Limiting Membrane.

CHANGES IN THE RETINA ON EXPOSURE TO LIGHT

A light stimulus falling on the retina causes a number of changes to occur which may be classed as structural, physical, chemical and physiological.

STRUCTURAL CHANGES occur on exposure of the eye to light : firstly, move-

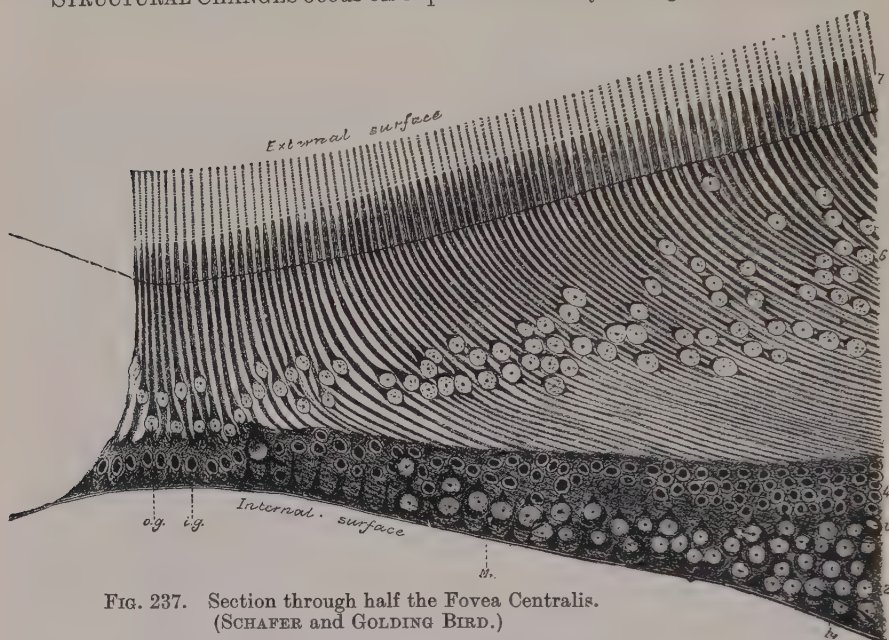


FIG. 237. Section through half the Fovea Centralis.
(SCHAFER AND GOLDING BIRD.)

ment of the pigment from the outer epithelial layer into the spaces between the rods and cones ; secondly, shortening of the cones themselves (Fig. 238). These changes occur only when the connections of the eye with the brain

A.

B.

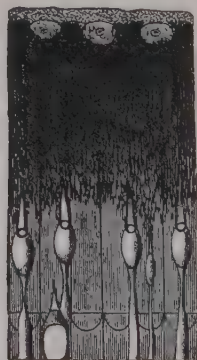


FIG. 238. Sections of the Frog's Retina.

A. Kept in the dark. B. After exposure to the light, showing retraction of the cones, and protrusion of the pigmented epithelium between the outer limbs of the rods. (ENGELMANN.)

are intact. The rate of movement appears to vary with intensity, and violet light is said to be better than red. It is interesting to find that electrical stimulation of the optic nerve or the falling of light on the other retina to that of the eye observed, also causes these cone movements. It

is supposed that the impulses which effect these movements travel through the nerve fibres already described as descending from the brain to the retina; it is for this reason that Engelmann called these fibres 'retinomotor.'

Other structural changes that are found, by histological investigation, to follow exposure of the retina to light, are swelling of the outer limbs of the rods, and the disappearance of chromatin granules from the ganglion cells. Both these changes are said to occur more rapidly under the action of rays of short wavelength.

PHYSICAL CHANGES are also found when the retina is stimulated by light, namely an electrical response somewhat similar to the current of action in nerve. A typical curve is shown in Fig. 239. A study of the electric response to lights of different colours and intensities has given the following results. With light of any one colour, a geometric rise of intensity causes an arithmetic increase in the current. With coloured rays of apparent equal intensity, yellow rays are said to give a larger current in the light adapted eye, and green in the dark adapted eye. It is interesting to observe that the current commences after a latent period, which is of the same order as that found for the perception of light by the eye. This and other facts mentioned above, would seem to point to the currents

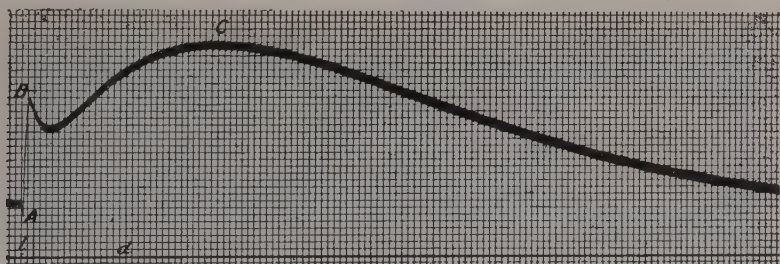


FIG. 239. Electrical Variation in Frog's Eye as recorded by the String Galvanometer. (EINTHOVEN and JOLLY.) On exposure to a single flash.

observed being the accompaniment of the passage of the nervous impulses to the brain.

CHEMICAL CHANGES in the retina on exposure to light are of two kinds, firstly a tendency of the retina as a whole to become acid in reaction, as shown in the change in its behaviour to certain stains; and secondly the bleaching of two pigments, namely the *visual purple* and *fuscin*. With regard to visual purple (or rhodopsin) a large number of facts have been made out. In the first place it is found in association with the rod retinal structures only, and is therefore absent from the human fovea centralis. It is bleached on exposure to light, both in the retina and also in solution. The absorption of light by visual purple is greatest for the middle of the spectrum; the transmitted colour is therefore composed principally of red and violet rays. Small variations of colour are found, however, in samples obtained from different animals; some are even rose-pink in colour. In the second place the most potent colours in producing bleaching are those near the centre of the spectrum, that is the rays which are most strongly absorbed. This pigment therefore obeys Draper's law, which states that those rays that are absorbed are those which produce chemical change.

It will be shown below that the retina when adapted for vision in dim light is not only colour blind, but also that the green rays of the spectrum appear to have the maximum luminosity. It will be also shown that the rod-containing parts of the retina, where visual purple is to be found,

are the only regions that react to light of low intensity. Moreover the curve which represents the rate of bleaching of visual purple by rays of different colour is very similar in shape to that which shows the visibility of lights of low intensity, as in Fig. 240. The obvious inference is that visual purple is concerned with twilight vision. When the visual purple in the retina has been bleached by exposure to light, there follows a gradual re-formation of purple, which is independent of nerve connections, but occurs only so long as the stratum pigmenti is in contact with the rod epithelial layer. If we suppose that the product formed by the bleaching of the visual purple stimulates the rod apparatus, causing it to send impulses to the brain, we have a plausible hypothesis of the mechanism for night vision. This we may briefly describe as follows:—When light falls on the retina, certain rays, particularly those near the middle of the spectrum, are absorbed by the visual purple. The pigment is

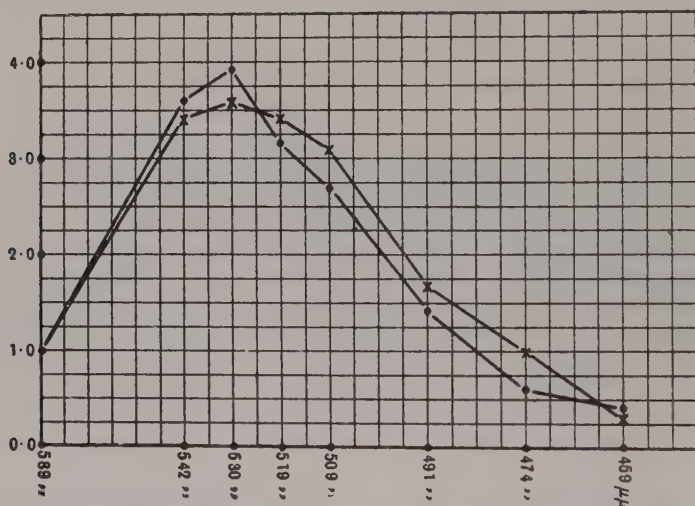


FIG. 240. Shows the Similarity between the Curve representing the Rate of Bleaching of Visual Purple by Light of different Wavelengths and the Luminosity Curve of Twilight Vision.

bleached in proportion to the light absorbed, forming a new product: this acts on the rods, causing them to send impulses to the brain which continue so long as the light falls. When the light stops the stimulating product is no longer formed, therefore the stimulus to the rods ceases.

The work of Hecht (1920-21) is very strongly in favour of such a view. He has shown that the rate of bleaching of a solution of visual purple by light, and the rate of light adaptation of the human eye both follow a logarithmic law: that is, the 'reaction' in both cases appears to be one involving the splitting up of a single large molecule into components. On the other hand, the rate of dark adaptation of the human eye follows a curve similar in shape to that given by a bimolecular reaction: that two molecules are interacting to form one. Taken in conjunction these pieces of evidence point most strongly to the conclusion that a single large molecule of visual purple splits under the action of light into two components, and that these when the light is removed combine again to re-form visual purple. Many analogous photochemical systems have been studied.

A picture, formed by the bleaching of the visual purple in those parts of the retina which correspond to the high lights of the image formed by the lens, can be fixed, much like a photograph, by immersing the retina in a solution of alum.

Fuscin is the pigment found in the form of needles, plates or prisms in the processes of the cells of the stratum pigmenti of the retina. The object of this pigment is apparently to absorb light, which might tend to spread, from those retinal elements on which an image of a light source is falling, to neighbouring ones. Some of this pigment is bleached by strong light, but so far as is known the break-down products have no visual function. The presence of other pigments has been described in the retina, such as visual yellow and the bright pigment granules found in birds. Their presence is too variable for them to be considered to take any essential part in the visual mechanism.

Physiological changes produced by light depend greatly on the region of the retina on which it falls, since this may contain rods only, cones only, both rods and cones, or neither rods nor cones. The peripheral parts of the retina contain numerous rods and very few cones. When stimulated by light of low intensity, this part of the retina is found to be exceedingly sensitive, particularly if the eyes have been closed or kept in the dark for a time. Tests with light of low intensity and of different colours, show that the region is colour blind, but that rays in the middle of the spectrum are more readily appreciated than others. We have here



FIG. 241. Look at Cross with Right Eye, hold Book at about 10 inches.

well developed the so-called 'twilight vision,' which is associated with the rod-visual purple mechanism just described. Besides being very sensitive to light of low intensity, the periphery of the eye is particularly perceptive of light of low intensity and short duration. This part of the retina, therefore, appreciates movement at night very readily. Lastly, owing to the fact that a number of rods connect with one nerve fibre conveying the impulses to the brain, the periphery of the retina has a poor perception of detail.

THE FOVEA CENTRALIS is found to contain cones only. The vision in this region is therefore the antithesis of that found at the periphery. The appreciation of light of low intensity is bad, but when an image is sufficiently bright to cause stimulation, its colour is perceived. When light is poor, rapid motion is not so well observed as it is by the periphery. There is an extraordinary acuteness in perceiving fine detail. This is due to the fact that the cones in the fovea are very closely packed, so closely that they become flattened where they touch one another and thus have a hexagonal shape in transverse section. Further, each cone is connected to its own nerve fibre, so that no cyphering of the impulses can occur on the way to the brain. Experiments on visual acuity definitely show that the fineness of the detail, which the eye can perceive at the foveal region, is fully as great as that which we should expect to find, if each cone acted quite independently of its neighbours. Parts of the retina around the macula lutea, since they contain both rods and cones, possess, as we should expect, both the power to perceive

colour found at the fovea and the ability to react to light of low intensity, without colour vision, which is possessed by the periphery of the retina. The presence of rods scattered between the cones, however, naturally impairs to some extent the appreciation of fine detail.

At the white papilla where the optic nerve enters the eye, there are neither rods nor cones, and therefore, as we should expect, this region is quite blind. This fact can be readily proved by looking with the right eye at the cross in Fig. 241. If now the book be held about 10 inches from the eye, the white disc will be found to disappear. By a simple calculation, it is found that the disc corresponds with the papilla of the optic nerve.

THE VISUAL FIELDS. Since the appearance of an external object will vary to a considerable extent, according to the region of the retina on which its image falls, it is a matter of considerable interest to determine the positions at which the appearances undergo change. This is also of practical value because the positions are found to be affected by disease. The determinations are usually made by means of an instrument called a *perimeter*.

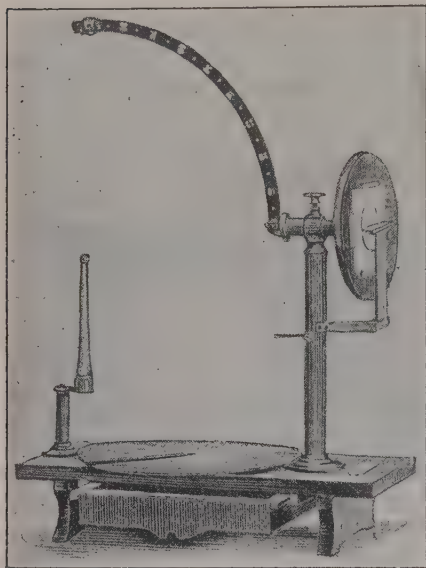


FIG. 242. Priestly Smith's Perimeter.

disc 2 mm. in diameter, either of white or of coloured paper, according to whether the rod or cone area is to be examined.

The results obtained by means of this instrument are shown in Fig. 243 which gives a typical curve for the right eye. The shaded area on the diagram is due to the obstruction of the eyebrow, nose and cheek of the patient. The visual field on the outer side will be seen to extend actually 14 degrees beyond the right angle. This result, which at first sight appears to be impossible, is in fact due to the considerable refraction of the light rays that occurs at the extreme edge of the cornea. The direction of the beam of light entering the eye under these circumstances is shown in Fig. 244 X below.

It will be observed that, even when looking straight in front, a man can see to a considerable angle behind himself. By deviating the eyes only slightly to either side, this angle can be increased to 40 degrees in the average case as shown at Fig. 244 Z. This ability to see to a considerable extent behind him is due to the narrowness of the head between the frontal processes and zygomatic bones. In those animals in which the eyes are placed on the sides of the head, and the visual axes are diametrically opposite to one

This consists (Fig. 242) of a metal arm bent to the segment of a circle. This is so mounted in relationship to a horizontal bearing that the segment always has its centre in correspondence with a fixed pointer which is seen on the left of the diagram. If the eye of the patient is applied close to this pointer and looks towards the centre of the bearing, the degrees marked on the metal segment show the actual angle at which an index is situated in relationship to the eye axis, no matter in what meridian the metal segment may lie. The index mark usually consists of a

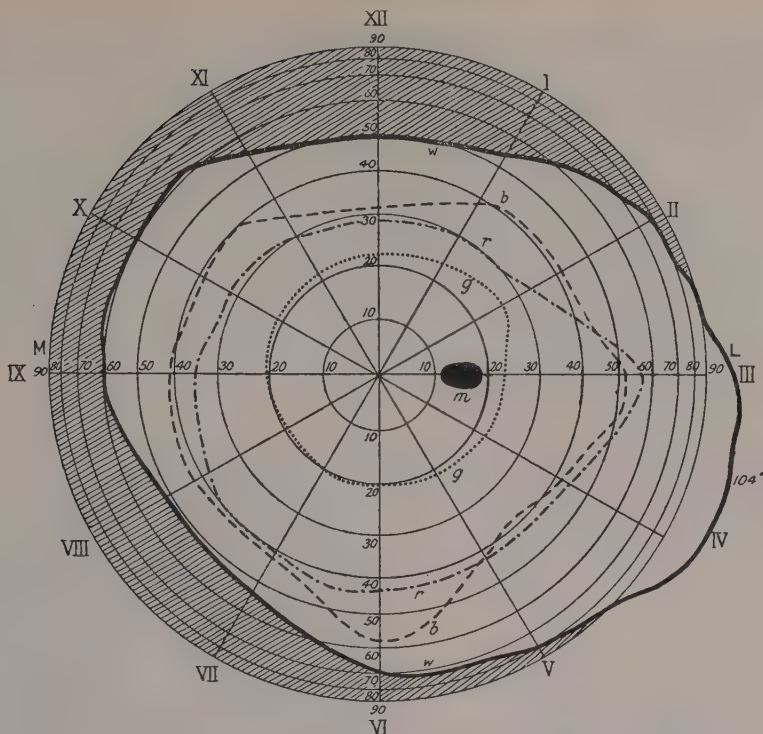


FIG. 243. Field of Vision for White and Colours of a normal Right Eye as obtained by the Perimeter. (HARTRIDGE.)

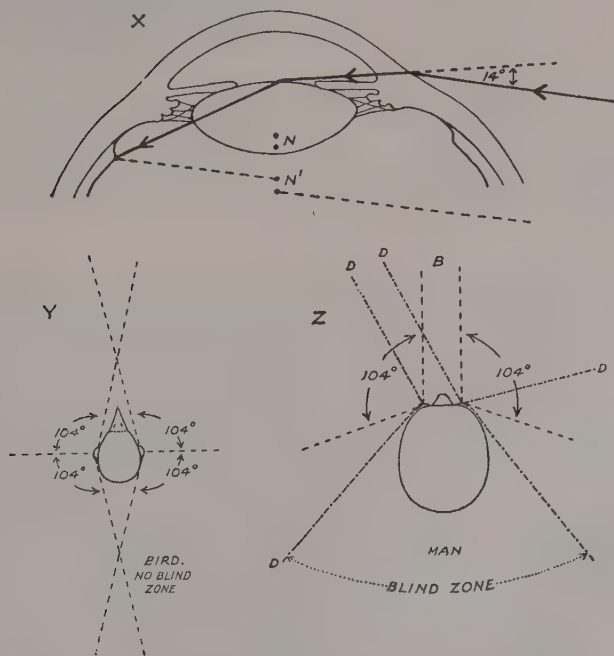


FIG. 244. Diagram Z shows Size of Blind Zone in Man. Diagram X shows how Rays from the extreme Periphery enter the Eye and reach the Retina. Diagram Y shows Absence of Blind Zone in Birds and certain Animals. (HARTRIDGE.)

another, the visual fields will actually overlap a short distance from the head, so that there will be no direction from which an enemy can attack without being observed (Fig. 244 Y).

UTILITY OF PERIPHERAL VISION. The high visual acuity of the fovea, and the great facility with which the eyes can be directed so that images form on this region, might raise the question as to the utility of peripheral vision. This question may be investigated experimentally by placing restricting screens in front of the eyes, or by ascertaining the experience of persons who are suffering from blindness in the periphery as the result of disease, *e.g.* retinitis pigmentosa. Both methods show that the periphery is of great value in directing attention to outlying obstacles. Our attention being excited we direct the gaze in the direction indicated, in order to bring into action the greater power of analysis of the fovea.

CENTRAL CONNECTIONS OF THE RETINA. The nerve paths by which the retina, itself a part of the central nervous system, connects with other parts of the central nervous system has been considered in detail in Chapter XVIII. Briefly the optic nerves from the two retinæ converge and join at the chiasma. These fibres from the nasal halves of both retinæ cross, so that the optic tracts which convey the impulses from the chiasma to their destinations contain fibres which have

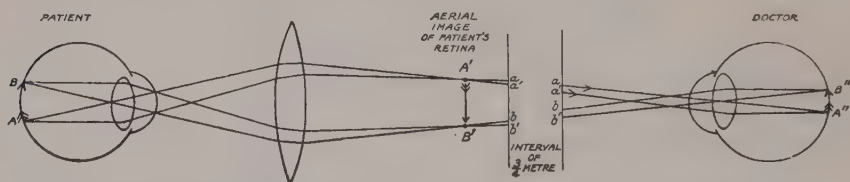


Fig. 245. Diagram to show Paths of Rays from Eye of Patient to Observer when the Indirect Method of Ophthalmoscopy is in use. (HARTTRIDGE.)

come from the same side of the retinæ as that to which they themselves belong. The right-hand tract has fibres from the right-hand halves of both retinæ. The fibres pass chiefly to the calcarine region of the cerebral cortex *viâ* the lowest part of the optic thalamus and the most posterior part of the cornea radiata for the sense of sight. But some pass *viâ* the superior corpora quadrigemina to the nuclei of the oculomotor nerves, thus causing reflex eye movements.

THE OPHTHALMOSCOPE. If the retina of a patient be illuminated by causing a beam of light to enter the pupil, the reflected light will cause the interior surface of the retina to be visible. In order to see the image distinctly, it is necessary either that both the eye of the patient and also that of the observer should be focussed for infinity (the direct method) or that both eyes should be focussed for one and the same intermediate plane (the indirect method). Both methods should be practised, since the indirect method gives a low magnification while the direct method gives a high one. The indirect method is carried out as follows:—A bright source of light having been placed behind and slightly to one side of the patient, the observer standing about half a metre in front of him reflects by means of a concave mirror an image of the light into his pupil. At the centre of the mirror is an aperture through which he sees the light which is reflected back from the patient's retina. The observer now holds a biconvex lens of about 6 cm. focal length about 8 cm. in front of the patient's eye, while he still directs the beam of light into the pupil as before. The image of the retina, which would normally be focussed by the lens system of the patient's eye at infinity, is now brought to a focus by the convex lens, forming what is called an aerial image (see Fig. 245). It is this image that the observer sees (Fig. 246), and in it are shown all the particular features of the vessels and nerves of the patient's retina. Beside its very great utility to the oculist, the ophthalmoscope is a very valuable instrument to the physician, for retinal vessels and nerves frequently show the evidences of constitutional disease,

which are of great assistance to diagnosis. Ophthalmoscopes are usually fitted with a number of small lenses of graduated power, which may be introduced as required behind the mirror. For the indirect method they are seldom required. The magnification of the retina given by the indirect method is usually about 3, while that provided by the direct is 12. If a higher magnification is an advantage it may be obtained by the above method by using a biconvex lens of longer focal length (say 12 cm.).

The image seen by the direct method is erect, that by the indirect is inverted.

On examining the back of the eyeball by either of these methods, the most prominent object is the optic disc or optic nerve papilla, which marks the point of entrance of the optic nerve. It is seen as a pale oval disc surrounded by a deep red background (Fig. 246). From the middle of the papilla the retinal vessels pass into the eyeball, and they are seen diverging from the papilla to ramify over the rest of the retina. The arteries can be distinguished from the veins by their brighter red colour as well as by the stronger reflection of light from their surfaces. The yellow spot is very difficult to see,

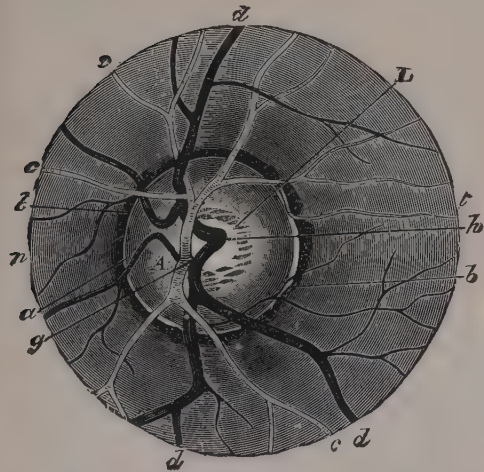


FIG. 246. Ophthalmoscopic View of Fundus of Eye, showing the Optic Disc, or point of entry of the Optic Nerve, with the Retinal Vessels branching from its centre.

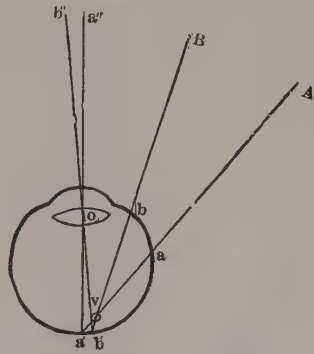


FIG. 247. Diagram of the Path of the Rays of Light in the Formation of Purkinje's Figures.

v represents a retinal vessel. When this is illuminated from A, a shadow is formed on the hinder layers of the retina at a'. This is projected along a line passing through the optic axis, and appears to come from a point (a'') on the wall. On moving the light from A to B, the image of the vessel appears to move from a'' to b''.

except in atropinised eyes, since it comes into view only when the observed eye is looking straight into the ophthalmoscope. Under these conditions there is a strong 'light reflex,' and the pupil contracts up to a pin-point, unless paralysed by means of atropine. In order to see the blind spot, or optic disc, the observed eye must be directed inwards; thus if A is looking at the right eye of B, B must be told to look over A's right shoulder.

By projecting a highly concentrated beam of light on to the side of the eyeball, it is possible to cause sufficient light to pass through the wall for the retina to perceive the stimulus. When that is the case, it is found that the retinal arteries and veins are seen as dark images on a bright ground (Purkinje's figures). By moving the point of illumination and then measuring the apparent shift of the vessels which occurs, it has been found possible to estimate the depth below the vessels at which the receptive surface of the retina is placed, namely 0.17 to 0.36 mm. Now the average distance between the vessels and the layer of rods and cones is found to be 0.2 to 0.3 mm.; it must therefore be the layer of rods and cones which forms the sensitive layer. The directions taken by the light rays are shown in Fig. 247.

Another method of viewing the vessels in one's own eye is to look through a small hole in a metal plate at a smooth white surface. On oscillating the aperture in relationship with the pupil about once a second, the vessels will be seen as shadows on the bright background.

8.—THE RELATIONSHIP BETWEEN STIMULUS AND SENSATION

Since we are unable to express our sensations in terms of physical units (we cannot say, for example, when one source is twice as bright as another), two methods of investigation are alone available, namely that which involves the determination of threshold values, and that which depends on the making of comparisons.

In order that a source of light shall be perceived, the image which is formed on the retina must have certain properties. In the first place, it must last for a certain finite time, for if it be of shorter duration than this it will not be perceived. Secondly, it must be larger than a certain size. Thirdly, its intensity must be greater than a certain limiting quantity.

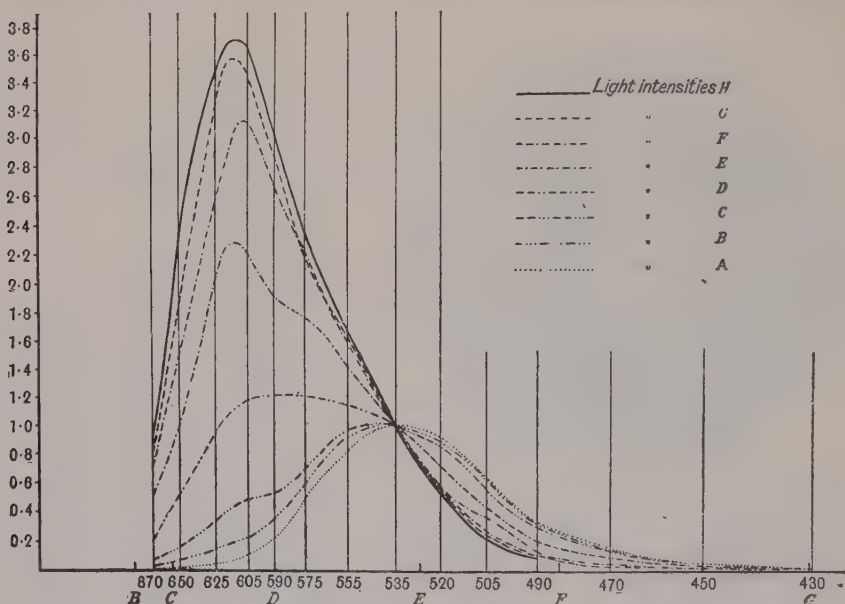


FIG. 248. Luminosity Curves for Spectra of different Intensity. (KÖNIG).

A = highest; H = lowest; Abscissæ = wavelengths; Ordinates = luminosities. The maximum of curve for light of high intensity is seen to be at 6100 A.U., that at low intensity 5150 A.U.

Fourthly, the rays it emits must have wavelengths which lie between certain limits. So that in the case of each of these four properties there are limiting values which must be exceeded; these values are called thresholds. The retina has, distributed over its surface, two different types of sensitive organ: the cone apparatus, which has the function of perceiving colours and is used in day vision; and the rod-visual purple apparatus, which is colour blind but very sensitive to light of low intensity and therefore used for twilight vision. Owing to the fact that the distribution of these organs is not uniform, we have to state the part of the retina which is being stimulated, when assigning a value to any of the above-mentioned thresholds. For example, the threshold for intensity may be that which just actuates the rods, that is the achromatic limit, or that which is sufficient to affect the cones and therefore causes an appreciation of colour. Moreover the value of any one threshold is to a considerable extent controlled by the value of the other factors which have been mentioned; for example, the time threshold

is shorter the greater the size and intensity of the light source. The exact conditions must therefore be carefully stated in quoting the value of a threshold. Lastly, we must consider the personal equation of the observer, and also the state of his vision, for both are affected to an important extent by constitution, health, fatigue, &c.

INTENSITY THRESHOLD FOR LIGHT (ACHROMATIC). If a spectrum be gradually reduced in intensity, it loses its colour and finally appears to the eye as a bright band which has its greatest luminosity in the green region of the spectrum and gradually fades towards both the red and violet ends. Since the band is colourless, any one part may be matched by any other part by suitably adjusting the intensities. But compared with the appearance under ordinary intensity, the red region of the spectrum has become greatly reduced in visibility, while the blue has become relatively brighter. The part of the spectrum with maximum luminosity is found to be the yellow when the intensity is high, but to be

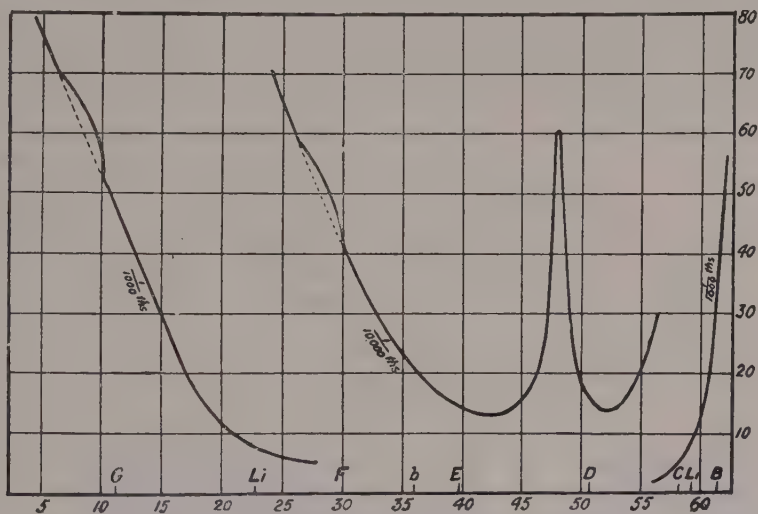


FIG. 249. 'Extinction of Colour' Curve. (ABNEY.)

Abscissæ = wavelengths; Ordinates = intensity in candle feet when colour just vanishes.

the green when it is low. It is therefore this shifting of the position of the maximum in the spectrum which has caused red to darken and blue to become lighter. The relative forms and positions of the luminosity (apparent brightness) curves for spectra of various intensities are shown in Fig. 249. If the spectrum of low intensity be still further decreased, a point will be reached at which the different parts become invisible to the eye; this will occur first with the ends, and last with the middle (at about 5271 A.U.). It is found, however, that the intensity values at which visibility ceases decrease the longer the eye is kept in the dark, that is to say the retina gradually becomes 'dark adapted.' The curves obtained for different degrees of dark adaptation are also shown in Fig. 249.

We must now consider the effects on the achromatic threshold, of size of light source, duration of stimulus and part of retina illuminated. With regard to size, experiment shows that, as the size of the source decreases, so the intensity at which extinction occurs increases, in fact that the area of the source multiplied by its intensity is a constant. With regard to the region of the retina that is stimulated, it is found that the rod-visual purple apparatus

is responsible for the appreciation of the light of low intensity ; it is therefore found in all parts of the retina other than the fovea centralis from which rods are absent. The effect of time of stimulus will be considered shortly.

INTENSITY THRESHOLD FOR COLOUR. If a spectrum of low intensity, which appears colourless to the eye, be gradually increased in brightness, a point will be reached at which the colours begin to be recognisable, first yellow and green, then blue and lastly red and violet. If the intensity at which the colour just vanishes is measured, the curve obtained is similar to that shown in Fig. 249. As the intensity is increased, the point of maximum luminosity gradually shifts from the green to the yellow. As light is gradually increased in intensity, an object is first seen without colour, but after an interval the colour also is recognised ; this is called the photo-chromatic interval. It follows from what we have said that the interval is greatest for colours of short wavelength (blue) and least for long (red) (the Purkinje phenomenon). The thresholds for light and colour differ in another important respect : whereas that of light varies with the degree of dark adaptation, that of colour is found by experiment to be nearly constant. With regard to the effect of area of light source, it is found that the same type of relationship exists in the case of colour as for light : that, as the area is diminished, so the intensity must be

correspondingly increased. The area and intensity, multiplied together, do not, however, equal a constant as they do in the case of light. The appreciation of colour is associated with the cones and is therefore most highly developed at the fovea. As the periphery of the retina is approached, the number of the cones very rapidly decreases, and we should therefore expect to find a limit to the size of the visual field for different colours. This may be tested by means of the perimeter (Fig. 242) and small coloured discs, or more accurately by suitable apparatus for employing spectral colours. By these methods it is found that the colour fields are smaller than those for light, but more or less concentric with them

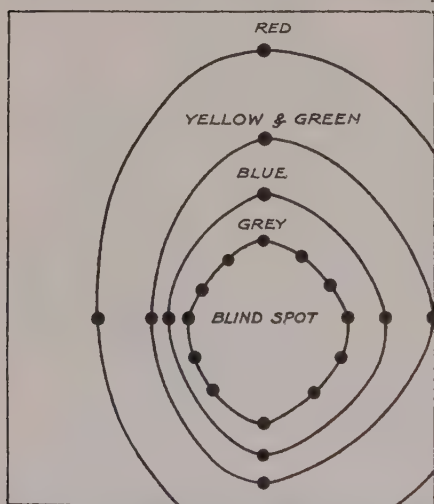


FIG. 250. Limitation of Colour Fields round the Blind Spot. (HAYCRAFT.)

(Fig. 243). The actual size of the fields varies with the intensity and size of the test light source or object. The order in which the colours disappear varies somewhat, but appears to be usually as follows :—First green, then yellow, then red, and lastly blue. The determination of the size of the colour fields is a technique of considerable practical importance, because they are found to become restricted in those progressive lesions of the optic nerves which may finally lead to total blindness, and also in inflammatory conditions of the retina and chorioid. Careful examination of the apparent limits of the blind spot by means of similar apparatus, was found by Haycraft to show that there is a similar variation in the relative sizes of the fields for different colours (Fig. 250). The same phenomenon is also found round the blind spots formed in the retina by disease.

SIZE THRESHOLD OR VISUAL ACUITY. If a small source of light be gradually reduced in size, a point is soon reached at which it becomes invisible. If it is a coloured source, it as a rule shows a well-marked photochromatic interval, that is, it first loses its colour and then disappears later. If the intensity of the source is very great, the size has to be much reduced before it becomes invisible: it is because of this that we see the stars. If the size and intensity at the point of disappearance be measured, it is found that when multiplied together they give a constant, so that as in the case of the light threshold, the determining factor appears to be the amount of light which falls on the retina. In the case of intermittent illumination a similar relationship is found.

Visual acuity is the ability to see as separate the images of small bright light sources of any shape placed very close together. Experiment shows that the distance between the sources must be increased as their distance from the eye is increased: in other words that the angle which they make at the eye must be greater than a certain limiting value. The angle usually obtained is an angle of one minute, and on this the lettering used in practice for testing the visual acuity of patients is based (see page 413). Persons with exceptionally good vision are able to see the separate images when the angle which the sources make at the eye is very much less than this, namely 24 seconds. Assuming that the posterior nodal point is 15.6 mm. from the retina (this being the distance in the normal eye), 24 seconds corresponds to a distance between the images at the retina of 0.0018 mm. The diameter of the cones is between 0.0020 and 0.0030 mm., and in the fovea they are very closely packed. The maximum visual acuity is therefore certainly as great as the size of the cones would lead us to suppose possible.

A dark spot on a bright ground is similar to the case just considered, because for the dark spot to be recognised it must subtend at the eye the minimal angle mentioned above. But increasing the intensity of the ground or the blackness of the spot will only make a very small difference, so that unlike the bright spot, an increase in the intensity does not make up for a difference of size.

TIME THRESHOLD. In considering the time threshold, two different sets of conditions require description: firstly, the minimum time during which a given stimulus must act in order to reach consciousness, and secondly, the minimum rate at which a series of stimuli must follow one another in order to give a uniform impression without flicker. Both are of considerable importance, since the first enters into such problems as the determination of the length of time during which a lighthouse beam should be caused to travel in a given direction; the second because it gives a reliable method of comparing the intensity of lights of different colour. Experimental investigation of the first type of time threshold is effected by measuring the length of stimulus necessary to cause a source of a certain intensity to affect the retina; and it is found that the lower the intensity the longer must the image fall on the retina. But if the eye be dark adapted, if the time and the intensity values be multiplied together, then within limits a constant is obtained. On the other hand, in the light adapted eye, the value is found to vary somewhat, but is sufficiently constant to show that the relation between intensity and time is approximately the same. Within limits, therefore, we find that at the threshold the total amount of light is constant, whether it be of high intensity for a very short period of time, or of low intensity for a correspondingly longer one. This relationship ceases to be true if the time of stimulation is longer than about one-tenth of a second, and this is

apparently due to the fact that the retinal apparatus reaches a steady state in about one-quarter of a second in the dark adapted eye (rod-visual purple apparatus). A lighthouse flash should therefore be visible to the eye for this length of time, in order to make the greatest possible impression. For coloured lights, approximately the same values are found, provided that allowance is made for the comparative intensity of the colour. Since the time required for the retina to reach a steady state is nearly that at which a series of stimuli must fall on the retina in order to produce a uniform sensation, for intensities near the threshold the rate at which flicker disappears is one stimulus every quarter of a second. But it is found that as the intensity rises, the rate must be increased in order to abolish flicker. The rule which most nearly expresses the relation appears to be that geometrical increase in the intensity requires an arithmetical increase in the rate. Sherrington showed, however, that the results are affected by simultaneous contrast. This phenomenon of flicker is, as I have said, used in practice for measuring the intensities of light sources. Two methods are employed, firstly, that in which the two light sources to be compared are measured separately for the intensity at which flicker ceases when the same rate of stimulation is used for both; and secondly, that in which the two sources are caused to fall alternately on the eye, and are adjusted in intensity until flicker ceases. Of the two methods, the latter is the more accurate. The value of these methods lies in the fact that they measure brightness independently of colour. The shape of the curves obtained by plotting the luminosity of different parts of the spectrum has been shown in Fig. 248.

Lastly, we have to consider the relationship between time intensity and apparent brightness, in the case of an intermittent source, the rate of which is sufficiently great to avoid flicker. Experiment shows that the brightness increases in proportion as either the intensity or the time intervals are increased, and further that equal brightness is obtained if the time multiplied by the intensity is constant. This statement is true of both the cone and the rod apparatus, and is known as the Talbot Plateau Law. Use is made of this law in the sector method of controlling intensity (see p. 435) because the intensity is proportional to the time during which the light is allowed to pass through, which is in its turn controlled by the angle between the blades of the sector.

COLOUR THRESHOLD. On testing the violet end with a photographic process, or the red end by a thermopile, it can readily be shown that the spectrum extends at both ends far beyond the visible limit. The visible limit at the red end under the most favourable conditions has been found to be 8350 A.U., while under ordinary circumstances it is difficult to go beyond 8000 A.U. Since rays beyond this reach the retina in considerable amount, the limit cannot be caused by opacity of the eye media, and must therefore be due to an actual inability on the part of the retina to record their presence.

Of several hypotheses which might be advanced for this inability, the most probable is that the retinal pigments are unable to absorb rays in the infra-red part of the spectrum, and therefore, according to Draper's law such rays cannot produce photochemical change and cannot be perceived by the eye. It may be mentioned in this connection that few organic pigments absorb strongly in the infra-red.

The limit at the violet end is less easy to determine, because the eye media, in common with a large number of other bodies, have the property of fluorescing when the ultra-violet rays fall on them, *i.e.* they convert them into rays of longer wavelength and therefore make them visible. The

resulting impression is, however, quite different because, since these rays are generated in the eye media themselves, they are spread over the retina as a haze without there being any proper image formation. The limit of the visibility of the violet end of the spectrum appears to be at about 3800 A.U., while the portion which is seen because of the fluorescence, which it produces, and which appears a pale lavender, ends at about 3200 A.U. Since the wavelength of the extreme red rays is a little more than double that of the extreme violet, the eye is sensitive to a little over an octave. The range of appreciation of the eye is therefore very much smaller than that of the ear, which is about 10 octaves. As age increases, the eye media become yellow in colour; this change particularly affecting the lens, the violet end of the spectrum becomes shortened owing to absorption. On removing the lens of the eye as in an operation for cataract, the sensitiveness to the violet end of the spectrum is considerably increased. It would therefore seem certain that the limitation of the spectrum of the violet end is largely due to absorption by the eye media, and not to inappreciation on the part of the retina. The causes of the limitation of the two ends of the spectrum are therefore different.

DIFFERENCE THRESHOLDS. Beside the thresholds for light, colour, time and wavelength, which may be called absolute thresholds, there are certain difference thresholds that must be considered. Thus, for example, a certain finite difference must exist between the intensities of two sources of light of the same colour, for a difference between them to be appreciated by the eye. There are four principal types of difference threshold, that of intensity, that of colour, that of saturation, and that of size.

DIFFERENCE THRESHOLD OF INTENSITY. It is found by experiment that a just perceptible difference between the intensities of two surfaces varies with the mean value of their intensities. Thus, supposing that it had been found by one experiment that a difference of intensity of one foot candle was necessary in order that two sources should be just distinguishable, the average intensities of which were one hundred foot candles, then in another case in which the average was 25 F.C. the least perceptible difference would be found to be one-quarter F.C. This is one illustration of the principle known as Weber's law. It appears to be true for light of medium intensity, and for sources not separated by more than a small interval. But the least perceptible difference is found by most observers to be less than that taken for purposes of illustration above, namely one-hundredth part of the mean intensity; thus Helmholtz found it to be a $\frac{1}{100}$ th, other observers have obtained even smaller fractions. It is interesting to find that the results are not influenced by the size of the pupil.

DIFFERENCE THRESHOLD OF COLOUR. If the range of colours exhibited in the spectrum be carefully examined, it will be seen that there are certain parts, notably at the red and violet ends, at which the change of colour with wavelength is a very gradual one. At other parts, on the contrary, the change of hue is very rapid; the yellow region at 5800 A.U. may be given as example. If therefore we determine by experiment what difference of wavelength is just perceivable by the eye, we find that it varies with the part of the spectrum under observation. We may therefore conveniently express the difference threshold in different parts of the spectrum in the form of a curve, as in Fig. 251. In persons with normal vision the total number of different hues in the spectrum is calculated to be 165. In persons with colour blindness the number is greatly reduced.

This fact has been applied by Edridge Green for the detection of colour blindness; details of the method will be given later. It should be pointed

out that, since in this method the spectrum itself is presented to the observer, so that there is a gradual change from one colour to the next, it is the threshold of rate of change of colour that is determined, and not difference threshold of colour. Edridge Green's method gives only from 21 to 28 monochromatic patches in the spectrum.

DIFFERENCE THRESHOLD OF SATURATION. By saturation is meant the amount of white light which is present with, and is therefore diluting, a colour. The threshold would appear to be of the same order as that of intensity given above, namely that a difference in the amount of white light diluting a colour by $\frac{1}{160}$ th of the total intensity present can be just appreciated by the eye.

DIFFERENCE THRESHOLD OF SIZE. If two objects are the same distance from the eye, and are close to one another and in similar positions, a difference of one-hundredth the mean size can, as a rule, be appreciated. If they are at different distances from the eye, or are far apart, or are not in similar position

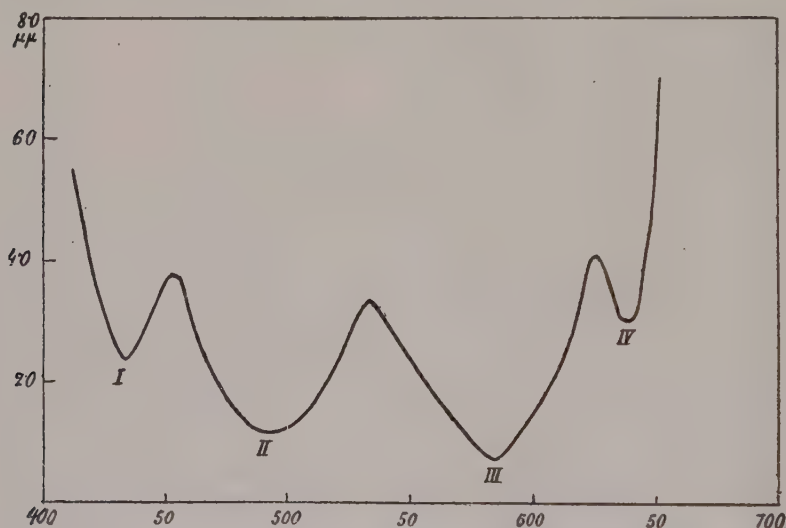


FIG. 251. Curve showing Difference Threshold for Colour at different parts of the Spectrum.

Abscissæ = wavelengths. Ordinates = difference between wavelengths capable of being discriminated. (STEINDLER.)

(e.g. one perpendicular and the other horizontal), then considerable errors may occur.

THE METHOD OF COMPARISONS. In the application of this method three different series of investigations have been carried out. (1) To determine the intensities of three primary colours which, when mixed together, will match the different spectral colours or white light. (2) To determine the intensities and wavelengths of the complementary colours. (3) To ascertain the intensities and wavelengths of red and green rays which, when mixed together, match a pure spectral yellow.

The colour box in some form or other is used for these tests. Abney's apparatus may be described as a typical example. Light from an arc lamp is focussed on to the slit of a powerful spectroscopie, which consists of a collimator, a train of prisms and a telescope. The spectrum thus produced is caused to fall on three slits, one of which corresponds with the red, another with the green, and the third with the blue. The light having passed through the slits falls on a lens which forms an image of the prism faces on a screen. The light from the slits thus recombines on the screen to produce a bright patch, the colour of which alters according to the intensities of the three com-

ponents. To one side of the patch a second patch of light can be thrown from the arc lamp, and this also may be varied in different ways according to the nature of the experiment. The intensities of the different beams could be modified by altering the widths of the slits; a preferable method is to employ rotating sectors, the angles between the blades of which can be varied at will (see Fig. 252).

Colour mixing experiments performed with this apparatus give results that have already been briefly considered in Section I. It is found that, not only do the three primary colours, when mixed together in the right proportions, form a white light that is indistinguishable from ordinary

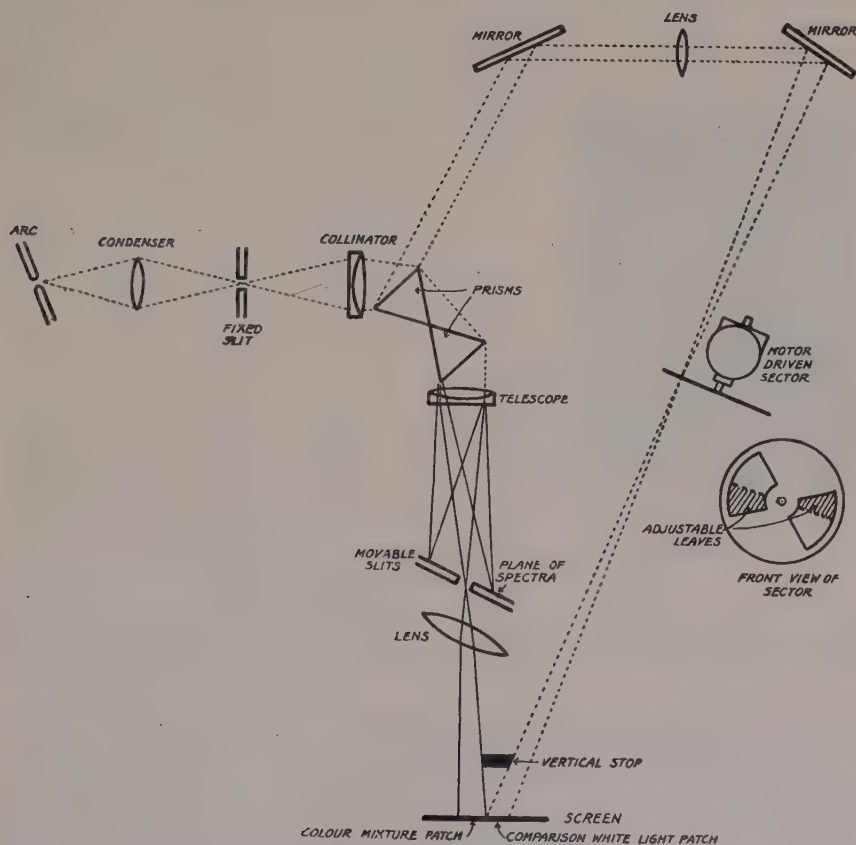


FIG. 252. Colour Patch Apparatus for Mixture and Comparison of pure Spectral Colours. (ABNEY.)

white light, but they can also be made to match the whole range of colours both of the spectrum and of pigments. It was also described how that certain pairs of colours when mixed in the right proportions are able to match white, and that these pairs are called complementary colours. If the colours that are mixed are further apart than are the complementary colours, then the mixed colour is found to be a shade of purple; but if nearer together than the complementaries, then the colour formed by the mixture corresponds to an intermediate part of the spectrum. Thus, if the colours mixed are red and green, the intermediate yellow and orange portions of the spectrum can be matched. As a rule the mixed colour is not so pure as the corresponding spectral colour, being less saturated (that is, diluted with

a certain amount of white light). The mixture of red and green is an exception because it is found that accurate matches with spectral yellow can be made if the green component be not shorter in wavelength than 5400 A.U. These facts can be expressed diagrammatically in the form of a geometrical figure, the colour triangle, in which the three fundamental colours occupy the corners and white the centre (see Fig. 211). Matches made by light of one intensity require readjustment if the intensity be changed, and matches made by one observer are different from those made by another. The variation with intensity is readily explained by the shifting of the centre of the luminosity curve from the yellow towards the green, as the intensity is lowered. The amount of red required in a match will become increasingly greater, and that of the blue less, as the intensity is lowered. The variation with the observer, when small, is explained by individual peculiarity in the pigmentation of the eye media or of the fovea centralis; but when considerable, by abnormality in the response of the retina to colours. Because of

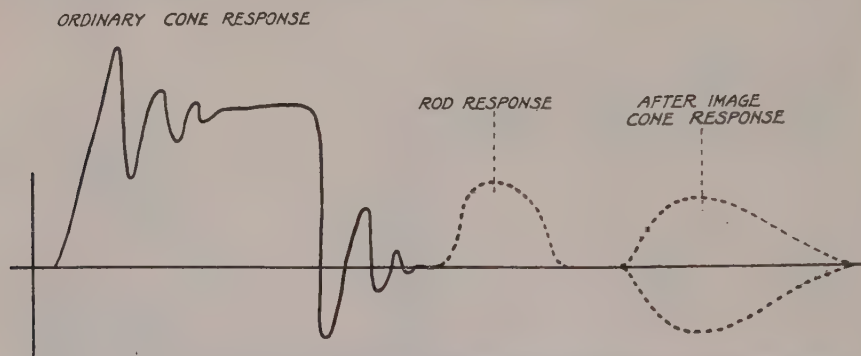


FIG. 253. Curve representing diagrammatically the Sensations aroused when the Eye has been Stimulated by a Flash of Light.

Intensity of Sensation vertical. Time horizontal. (HARRIDGE.)

this the method of colour mixtures forms a very valuable technique for the investigation of colour blindness.

THE FLICKER METHOD. The majority of observers can obtain consistent measurements of intensity with the above method only when the colours of the two patches are exactly alike. Thus it is difficult to adjust a green light to be of equal apparent brightness (luminosity) with a red because the difference in colour makes the judgment of brightness inaccurate. Abney found that in his own case practice greatly increased the certainty with which the measurement could be made. A more reliable technique is given by the flicker method. The two patches are viewed through a rotating sector, the speed of rotation of which can be controlled. The intensity of one of them is now adjusted so that, when the speed of the sector is altered, both commence to show and to cease showing flicker at the same time. By applying this method to the colour mixing apparatus, the luminosity of the different parts of the spectrum can be determined. The curves obtained at different luminosities have already been given in Fig. 248. Tested by this method, different observers show individual peculiarities, which amount in some cases to a greatly diminished perception of a certain part of the spectrum. Some of the types met with will be described later.

9.—THE SUBJECTIVE PHENOMENA OF VISION

By 'subjective' we mean that the sensations under consideration cannot be traced solely to the stimulus which initiated them. Thus at a certain rate, intermittent stimuli presented to the eye form a continuous sensation,

so that flicker appears to have ceased. But the carrying on of the sensation from one stimulus to the next is performed by some part of the visual mechanism, and has nothing to do with any physical peculiarity of the light. It is therefore an example of a subjective phenomenon.

THE SENSATION CURVE. When a light stimulus enters the eye a certain period of time elapses before a sensation is perceived. This latent period may be compared with that which occurs between the stimulus and contraction of a muscle. After its commencement the sensation rapidly rises to a maximum (see Fig. 253) and then shows several rapid fluctuations as it reaches its mean value. These fluctuations are called Charpentier's bands, and are well seen after stimulating the eye by means of the flash from an electric spark. They have been compared with the oscillations which occur when an electric current is passed down a telegraph cable, and which are caused by the inductance and capacity of the circuit. Similar oscillations occur when the telegraph circuit is broken; these oscillations also have been witnessed and described by Bidwell at the end of the primary visual response. The time taken for the sensation to reach its maximum varies from 0.16 to 0.07 secs., being shorter the greater the intensity of the stimulus. This so-called primary image is followed under certain conditions by a less definite and less intense image, which has the following characteristics: (1) It is not seen when the eye is light adapted. (2) It is strongest for green light, and is absent for red. (3) It is absent from the fovea. (4) It is not seen by persons suffering from night blindness. (5) It is always of a bluish-grey colour. All the above facts fit in with the view that, whereas the primary response corresponds with the reaction of the cones to the stimulus, the image which is sometimes seen to follow belongs to the rod apparatus.



FIG. 254. Charpentier's Bands as seen when a disc with a narrow radial slit is rotated in front of an illuminated screen about once a second.

THE AFTER IMAGE. Following these responses of the cone and rod end organs is the so-called secondary image, which certainly concerns the cones and may concern the rods as well. This image is of longer duration than those already considered, and it is of much lower intensity. It has, however, the peculiarity that, so long as it lasts, the part of the retina affected gives a diminished response to a stimulus of the same type as that which it had previously received. For example, if the first stimulus was one of white light, then a second white light stimulus falling in the period occupied by the after image of the first, would not be recorded by the retina with the normal intensity. It has been pointed out that the after image period in some ways resembles the refractory period which follows the activity of muscle and nerve. If the second stimulus affects a larger area of the retina than that affected by the first stimulus, then a dark patch is seen lying on a bright ground, the dark patch corresponding in size to the first stimulus, the bright ground corresponding in size to the second stimulus. If the first stimulus is coloured, and no stimulus follows, the secondary image is found to have the same colour; but if a second stimulus of the same colour, but rather larger size, falls on the retina during the secondary image, then, as before, a dark patch is seen lying on a bright coloured ground. If,

on the other hand, the second stimulus be one of white light, the sensation received is one of the complementary colour, the reason being that the red constituents of the white light are partially excluded by the after image of the first stimulus, but not so the other spectral colours, and the image which is seen is therefore a blue-green one. Because of these peculiar properties the after image is said to have two phases : being called positive when the eye receives no second stimulus, and the appearance of the after image is the same as that of the first stimulus ; and being called negative when, owing to the incidence of a second stimulus, the after image shows the opposite intensity or colour to the stimulus which originated it. Since absence of the second stimulus causes the after image to be positive and the presence of a second stimulus makes it appear negative, we should expect a second stimulus of the right intensity to cause the after image to disappear altogether, since it would stimulate the surrounding retina with the same intensity as does the after image of the first stimulus. Experiment shows that this result can be achieved. Because of the importance of these properties of the after image, we may with advantage recapitulate as follows :—As a result of a stimulus the region of the retina affected gives a response



FIG. 255.

which is followed by a second or after image. During this after image, this area is incapable of reacting with the normal intensity to a like stimulus, but shows increased excitability to a stimulus of the opposite kind. For example, after a green stimulus the retina is unable to respond fully to another green stimulus unless it falls either before or after the period of the after image. Therefore, if during that period a white stimulus be arranged to fall on the retina, it will cause a purple sensation (purple being white minus green) in that part of the retina first stimulated. The duration of the after image is variable, but is found to correspond roughly with the intensity and duration of the stimulus. Thus, after a few seconds' exposure to a bright light the after image may be noticeable for two or three minutes, its intensity waxing and waning in an irregular manner. Successive images are often found to show a series of colours ; a common series is bluish-green, violet, rose, and finally orange or green. The phenomenon is, however, very variable. The colours may be explained by assuming a difference in the rate of oscillation for the after images of the different colours. For example, the above series of colours would be obtained if green were more rapidly, and red less rapidly, perceived than blue.

FLICKER AND VISUAL PERSISTENCE. A study of the characteristics of the sensation curve provides an explanation of a number of the subjective phenomena of vision. For example, if a cardboard disc, marked as shown in Fig. 255, be caused to rotate slowly, while the black and white sectors are readily recognised, their radial margins appear blurred. This blurring is due to the slow rise and fall of the primary image of the sensation curve. If the speed be increased, a point is reached at which the disc gives an unpleasant glittering appearance ; this would appear to be due to one stimulus occurring during the after image of the previous one, and thus becoming

suppressed, but being followed in its turn by a fresh stimulus which is caused by contrast (see later) to have a greatly increased intensity. If the rate of rotation of the disc be still further increased, a point is reached at which a stimulus falls during the primary image of the previous one. The persistence of the primary image after the cessation of the stimulus causes the stimuli to fuse to give a uniform sensation without flicker, which may be compared with the complete tetanus of a muscle. Since the primary response is more abrupt the greater the intensity of the stimulus, a more rapid rate of rotation is required to produce fusion at high intensities than at low.

PERIODIC STIMULI. We have seen that, if a stimulus falls during the after image of a previous one, its character is altered. If the two stimuli are similar, the second stimulus tends to be suppressed, but if dissimilar the second stimulus appears to be increased. If, on the other hand, the second stimulus falls either before or after the after image, it appears to be unaffected. But the experiments on flicker show us more than this, because even in a case where a second stimulus comes before the after image of the first, it is clear that the third would at a certain speed coincide with it, and would therefore be modified. Experiment seems to show no evidence for such an effect, and we must therefore conclude that the occurrence of the second stimulus in some way inhibits the after image of the first, so that its results are not apparent. Further evidence for this view is to be obtained from continuous stimuli, for we do not find a sudden diminution in the intensity of the response a moment or two after a continuous stimulus has begun, such as we should expect if the after image of the commencement of stimulus were suddenly after a short interval to assert itself. What happens to these suppressed after images? Are they entirely destroyed, or are they caused to accumulate until the end of the stimulus? The evidence appears to be in favour of the latter view, because an after image has a more definite character the longer the stimulus. Moreover if the gaze be directed towards a fixation point, and the inclination to blink be rigidly suppressed, after a few seconds the images of objects which fall on the periphery of the retina begin to appear milky, particularly in the shadows. At the same time the brightness of the high lights seems to be reduced so that it approximates more and more closely to the milkiness of the shadows. When this stage is reached, objects appear in outline, the contours being produced and renewed by imperfect fixation. If fixation can be retained for a short period, it will be found that the whole field becomes blank with the exception of the fixation mark. If this also disappears momentarily, then fixation is lost, the eye makes an involuntary movement, and the whole field immediately fills with detail again. In this experiment, two processes seem to be going on: firstly, in the shadows, the disappearance of the after images of previous impressions, the replacement of the visual purple previously bleached, and possibly also the recovery of these parts of the retina from the effects of previous stimulation, all of which will increase the sensitiveness of the retina so that it now responds to the light reflected by the shadows; secondly, in the high lights, the accumulation of after images, the bleaching of the visual purple, and possibly the effects of fatigue, all of which tend to reduce the intensity of the impression. So that these processes, tending to increase the brightness in the shadows, and to decrease that of the high lights, finally bring them to the same level. In these processes the accumulation and removal of after images would appear to take a considerable part. The conclusion to which we are forced is, that at the beginning of a continuous stimulus, the after images are effectively removed until such time as the stimulus shall cease,

when they can be permitted to assert themselves. But if the stimulus be prolonged, the suppression becomes more and more difficult, until the accumulation of after images is so extensive that they begin to obtrude more and more on the impression conveyed to consciousness.

FATE OF AFTER IMAGES. If the conclusion drawn from the above experiments is valid, the question arises as to the apparent unimportance of the after image in ordinary vision. The answer is to be obtained from experiments like the following :—If fixation be continued until the images formed on the retina appear in outline as in the previous experiments, and the gaze be then quickly turned to a second fixation mark placed some distance from the first, it is found that, on returning to the first mark, some time has to elapse before the appearance in outline is obtained again ; in fact the time taken is not very different from that required to reach this stage at the beginning of a new experiment. The second impression had effected an almost complete removal of the after image of the first, so that on returning to the first again, the slate had, as it were, been wiped clean, and the first impression therefore acted as if it were a new one. This conclusion is entirely in agreement with our previous conclusions with regard to the after image, namely that it corresponds to a period in which a stimulus, similar to that to which the after image belongs, is inhibited, while that of a different kind is favoured. If, therefore, during fixation the gaze be momentarily directed elsewhere, the after image that had been set up is quenched by the new impression, and on returning the gaze to the fixation point the old image behaves almost like a new one. The non-intrusion of the after image in ordinary vision is therefore due to a considerable extent to the continual and rapid replacement of one impression by another, by the shifting of the gaze, and also to the spreading of the accumulation of partially effaced after images more or less uniformly over the retina. It has been suggested that impulses may be originated from the external eye muscles on movement, which on reaching the brain assist in the removal of the after images of previous stimulation.

ADAPTATION. If the eye after being in the dark is rapidly exposed to the light, at first the sight is confused and the eye dazzled, in spite of the powerful constriction of the pupils. The eye, however, very quickly becomes accustomed to the greater intensity, or, as we say, it becomes light adapted. In a similar manner, on entering the dark from the light, the eye can at first see nothing, but by degrees it becomes accustomed to the new conditions, and objects begin to be recognised : the eye has therefore become dark adapted. In the first case, the initial light stimulus reduced the sensitiveness of the eye to light to such an extent that the eye ceased to react to an excessive degree as it had done at first. Dark adaptation appears to consist of two separate processes : (1) the removal of after images from the cone light-receiving mechanism, and (2) the replacement of visual purple for the rod apparatus ; the former predominating at high intensities and the latter at low.

FATIGUE OF THE RETINA. If the eye has been exposed to a very bright light for a considerable time, there is at first inability to see with the dazzled part of the retina. If a field is looked at, a black spot appears to lie in front of it ; if, on the other hand, the field subsequently looked at is dark, this same area of the retina appears to be filled by a bright haze. If the dazzling light be restricted to one colour, there is an inability to see the same colour, if of lower intensity, immediately afterwards. The power to see other colours is apparently quite unaffected ; in fact Burch stated that the complementary colour actually appears to be more vivid than usual. These

changes are similar to those caused by after images. The negative after image causes diminished appreciation of colours similar to itself, while the positive shows itself as a bright image similar in colour to the original stimulus when a dark field is looked at.

CONTRAST PHENOMENA

SUCCESSIVE CONTRAST. Visual impressions are affected by the previous history of the retina ; thus, after the eyes have been directed towards a red surface, a grey surface appears to be tinted green, a green surface seems a more vivid colour than normal, while a red colour is relatively dull. In other words, after stimulation by one kind of source, another of a similar nature is inhibited, while that of a different nature is either unaffected or may be even increased. This effect is called successive contrast. Experiment shows that the change of the second stimulus is such that it favours the colour complementary to the first stimulus. These effects are similar to those already described under adaptation and fatigue, and the causation of the phenomenon is the same as that given above, being due to the presence of an after image.

SIMULTANEOUS CONTRAST. If the retina is stimulated by two separate impressions, any differences between the impressions will be found to be accentuated. Thus if a small grey surface be placed on a white ground, the grey will become darker, and to a less extent the white ground will become lighter. If now the same grey surface be placed on a dark ground, it will be found to become lighter and the field darker. The nearer the surfaces are together the greater are the effects of contrast, the edges showing the effects of contrast most. In the case of colours, similar changes take place : thus two similar colours of different intensity placed together appear to be more different ; two colours of different saturation change, the one to greater, the other to less saturation ; while two colours of different wave-length appear, under the influence of contrast, to suffer a variation towards the complementary colour. A similar change is observed if contrast is occurring between a colour and a grey surface of approximately the same intensity, for we find that the grey is obviously tinted with a colour that is very nearly the complementary of the colour in question. It has been stated that the light which reaches the eye other than through the pupil (*e.g.* the sclera) and which is coloured an orange-pink in consequence of its partial absorption by the blood pigment in the capillaries, is responsible for the contrast colours not being strictly complementary to those which produce them. It is also found that separation of the surfaces, or the demarcation of the junction of the two surfaces by means of a narrow black or white line, or even the existence of small marks or creases, reduces the effects of contrast to a considerable extent.

We can summarise the effects of simultaneous contrast in the following way :—if one part of the retina is being stimulated, the part surrounding it not only tends to discourage a similar stimulus but also favours one of a complementary nature (black in this connection being considered as complementary to white). But this statement is similar to that which we have already made with regard to the effects of the after image on the same part of the retina which has received stimulation. Simultaneous contrast would therefore appear to be simply an extension of the after image phenomenon into a region of the retina outside the confines of the original stimulus. Experiment shows that this extension does not go far from the excited area, for the contrast effects, which may be considerable near the contour, rapidly decrease as the distance from the contour increases.

BIDWELL'S EXPERIMENT. If a brief white light stimulus be caused to fall during the after image period of a previous red stimulus, we should expect the white light to be tinted blue-green, because red light is suppressed and its complementary increased. If the intensity and time intervals are carefully chosen, the blue-green sensation may be made stronger than the original red stimulus to which it owes its colour. The persistence of vision causes this blue-green response to last an appreciable time, and therefore if another red stimulus rapidly succeeds the white one (the one which is coloured blue-green) it will tend to be suppressed from consciousness. But a white stimulus succeeding this second red one will be coloured blue-green by its after image, because it has left its impression on the visual mechanism, although that impulse has not been conveyed to consciousness. If therefore a series of such red and white impulses be caused to fall on the retina, each white one will be tinted blue-green, and each red one will be suppressed, the result being that the complementary colour alone is seen. This interesting phenomenon was discovered by Bidwell.

He took a disc of tin plate about 8 inches in diameter,

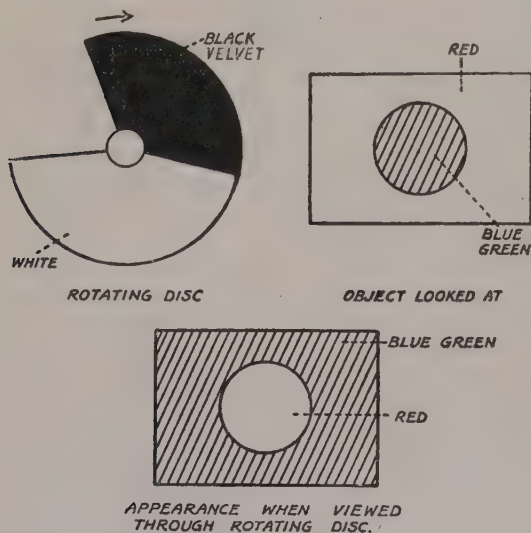


FIG. 256. Bidwell's Rotating Disc.

An object looked at through the disc appears in complementary colours.

and arranged so that it could be rotated by an electric motor 6 to 8 times a second. From this disc a sector was cut of approximately 60 degrees; half the remainder was covered with black velvet and the other half with white paper. Behind the disc were mounted two pieces of silk, one red, the other blue-green. The order in which the images were presented to the eye on rotation of the disc was: (1) coloured silks, (2) white sector, (3) black sector, and so on. The result was found to be that the red silk appeared pale blue-green, and the other pink; that is in both cases the complementary colour alone was seen. This experiment brings out very clearly the fact that the after image process is entirely subconscious. The following observations confirm this conclusion.

BURCH'S EXPERIMENT. It has been much discussed in the past whether contrast phenomena are due to errors of judgment, as Helmholtz supposed, or due to physical or physiological changes taking place in the retina or in the conducting paths leading from it to consciousness. Burch disproved Helmholtz' view by the following simple experiment. A box (Fig. 257) is divided into two long compartments, *a b* and *c d*. At *a* the compartment is closed by a red glass-plate and at *c* by a blue glass-plate. Apertures are provided at *b* and *d* for the observer's eyes. At + and + two small grey crosses are fixed about the middle of the compartment on sheets of transparent glass. On looking through the openings *b* and *d* and converging the eyeballs, so as to fix the point *o*, we get a fusion, more or

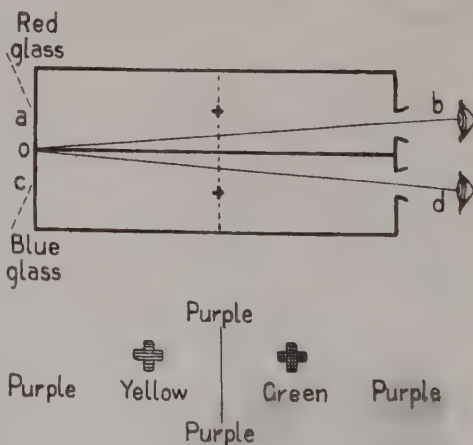


FIG. 257.

less complete, of the two colours red and blue, so that the background appears purple; or there may be a struggle between the colours, at one time blue, at another red predominating. To the judgment, however, there is one background and not two, and therefore, according to the theory of Helmholtz, the grey crosses should by contrast both acquire the same induced colour, which would be complementary for purple. But it is found that the two crosses are perfectly distinct in colour, that which is seen by the eye against the blue ground being yellow, while that on the red ground is green, showing that the phenomena of simultaneous contrast are not due to an error of judgment.

SHERRINGTON'S EXPERIMENT. The same fact is very definitely established by the following experiment devised by Sherrington. The disc (Fig. 258) presents two rings, each half-blue and half-black. The outer ring is intensified when at rest by simultaneous contrast, the black half being seen against the surrounding yellow, while the luminosity of the blue half is increased by the effect of the surrounding black. In the inner ring the blue half is darkened by contrast with the surrounding yellow, while the black half is not evident at all. If the disc be rotated, we get two concentric rings on an apparently homogeneous field. It is found however that the outer ring flickers long after complete fusion has taken place in the inner ring, showing that the stimulation of the retina by the outer ring is increased under the influence of contrast.

ALLEN'S MONOCULAR EXPERIMENTS. By means of two independent monochromatic illuminators, Allen illuminated one eye with a small flickering light source of one colour lying on a background of a large non-flickering source of another. He varied the rate of flicker until a smooth sensation was perceived. He then made the justifiable assumption that, when an increase in flicker rate is required for smoothness, it demonstrates an increase in the sensitiveness of the retina at that point and *vice versa*. Allen found that a red background caused a decreased sensitiveness of the retina to red, but an increased sensitiveness for green and blue. A green background on the other hand made green minus, but red and blue plus, while a monochromatic yellow background made both red and green minus, but blue plus. Now these results fit in exactly with older ones on simultaneous contrast. They show, however, more than these could do, namely that both facilitation and inhibition are at work. They show, moreover, a trichromatic subdivision of the spectrum such as Young's theory of colour vision postulates.

ALLEN'S BINOCULAR EXPERIMENTS. By a similar arrangement to that used above, the constant coloured field was presented to one eye, and the small flickering coloured source of light to the other eye. These experiments also demonstrate a trichromatic subdivision of the spectrum, since a stimulus of red, green or blue to one eye enhances the perception to the whole spectrum, but especially to the corresponding colour in the other eye; there being two invariable regions between these at 0.655 and 0.500μ respectively.

CAUSE OF AFTER IMAGE. Sherrington has shown that in the case of muscles there is what is called reciprocal innervation. Thus stimulation of the cortex which causes the contraction of one muscle also brings about a corresponding relaxation of its antagonist, in order that a rapid and economical motion may take place. The contraction and corresponding relaxation are therefore analogous to the response of one part of the retina, which is accompanied by an inhibition of the surrounding parts of the retina to the same kind of stimulus (simultaneous contrast). In a similar manner the inclination to extension, which is found to accompany the prolonged flexion of a limb, finds its analogy in the phenomena of after

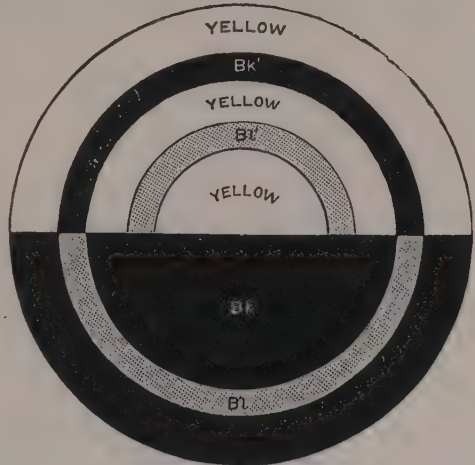


FIG. 258.

images and adaptation of the eye, since the tendency is to suppress a similar stimulus in the part of the retina stimulated and to encourage its complementary. The inference to be drawn from these analogies is that the after image and its allied phenomena are caused by changes in the conducting paths of visual impressions which are similar to those found to exist in paths belonging to the motor system. What the nature of these changes in the conducting paths may be is at the present time undecided. McDougall has suggested that they are fatigue effects in the synapses of the higher conducting paths. If this view is correct, it would seem difficult to explain why after images and contrast phenomena are best seen with a rested eye.

UTILITY OF THE AFTER IMAGE. We have seen that the effect of the after image is to inhibit the possible reception of a second stimulus, and at the same time to favour the reception of one of a different nature. The process is therefore one which favours change, for not only is there a tendency to efface an old impression but also to welcome a new one. Such effects must be of great value to an organ such as the eye, the function of which to a

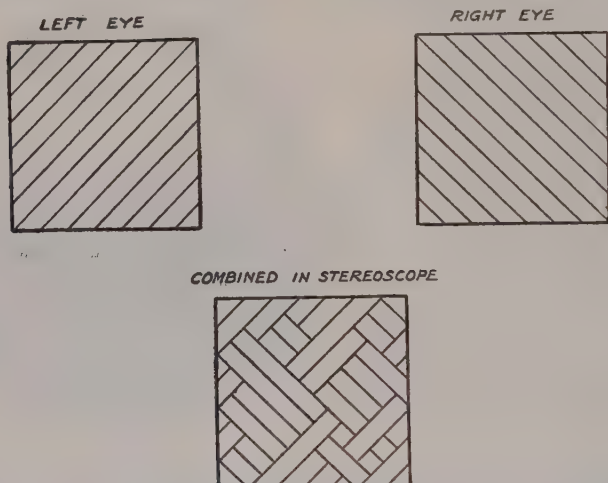


FIG. 259. Diagram to show how the Binocular Combination of two Dissimilar Images produces a Fluctuating Image containing parts of both of them.

considerable extent in everyday life is to present to consciousness the greatest number of impressions in a given time. For example, by measuring the time taken to read a passage in which almost every word was of importance, it was found that on an average eight words were read in each second, and that the eight words had an average of forty letters. It is clear from this that from eight to forty different impressions must be presented to consciousness in each second. The function of the after image in preparing the retina for the reception of new impressions would therefore appear to be a very important one. The effects of simultaneous contrast are equally important to vision, because the changes produced by it are such that the images falling on contiguous portions of the retina are made as unlike as possible. Not only are the intensity and colour of adjacent parts of the image made more definite (this process being comparable to the effects of intensification on a photograph), but the blurring at the edges of contours, due to imperfections in the image formed on the retina, is also largely eliminated (this comparing with retouching in photography).

BINOCULAR RIVALRY must be briefly referred to here, because of the similarity which it shows with the phenomena described above. If for any reason the images formed on

the retinae have dissimilar contours, rivalry ensues, first one image and then the other reaching consciousness. This process usually occurs independently in different parts of the field, so that the visual impression consists of a patchwork of the two images (Fig. 259). Seldom, if ever, are both images seen in the same part of the retina at the same time. It is found that a number of factors can cause one image totally to suppress the other: these are interest, novelty and brightness. The importance of this suppression can be appreciated by picturing the confusion which would occur if two different images were simultaneously presented to consciousness, as would happen in animals in which different images are formed in the two retinae and in cases of strabismus in man. The parallelism between this process and those which we have already described can be traced by regarding for one moment one of the images as the primary one. This causes impulses to travel to the visual centres unaffected at first by the effects of other images, but these tend to accumulate more and more until the primary image is overcome, and that of the other eye put in its place. But this image in time suffers in the same way, so that the images alternate. The fact that a new image can suppress an old one is due to the absence of after images in the first and their presence in the second. The predominance of a bright image can be explained by the longer time required for the after image to reach such a level as shall cause suppression. The preference for an image with contours would seem to be due to the greater ease with which the after image may be removed by small deflections of gaze.

10.—ERRORS OF APPRECIATION

Under this heading we include all types of abnormality in the retinal apparatus or in its central connections. The class therefore includes cases in which the image formed on the retina is in every way normal, and those in which the optical defects do not adequately explain the whole of the visual disability which experiment shows to be present. The class is found to include cases which range from slight impairment to complete blindness.

The following classification may be used:—

Group 1. Both rod and cone vision are affected, and there is thus both night blindness and total colour blindness.

Group 2. Rod vision is either affected alone, or there is slight defect in cone vision as well.

Group 3. Rod vision is unaffected, while cone vision is either altogether absent, or is found to show abnormality which affects certain colours only.

Note that any one of the above groups may be found to affect either one or both eyes, and may involve the whole or only a limited part of the retina.

COMPLETE BLINDNESS (group 1) may affect the whole of one or both eyes, or may occur in half the visual fields only. It may be limited to irregular-shaped islands or patches, or it may be found associated with central or peripheral vision. The shape of the affected area frequently gives a direct clue to the cause of the condition. The shape is best determined by means of the perimeter.

(a) The whole of one or both eyes is found to be blind. The disease may be congenital or may be the result of inflammation affecting the posterior parts of the eye (ophthalmoscope will confirm). Injury involving the whole of the optic nerve trunk will also cause blindness of the corresponding eye.

(b) The blindness involves the right or left halves of one or both retinae only. The lesion in such cases involves the optic tracts. Tumours are the commonest cause.

(c) The blindness is limited to a segment of the retina when the retinal vessels are affected (*e.g.* by embolism). The ophthalmoscope will confirm.

(d) Blindness which affects only the periphery of the retina is due either to deficiency of blood supply (as may occur in glaucoma), defective blood (severe anæmia), or the presence of poisons in the blood.

(e) If blindness affects chiefly the centre of the retina, the cause is probably poisoning by either tobacco, alcohol or both. At first vision is impaired

for certain colours only, but the blindness quickly becomes complete if the absorption of the poison continues.

(f) If irregular blind islands called *scotomata* are found in the visual fields, the cause may be inflammation of the chorioid or of the retina itself, or the detachment of the retina from the chorioid.

NIGHT BLINDNESS (group 2) is found in four different types of case.

(a) As an inherited condition. (b) In diseases of the liver in which bile salts are found to circulate in the blood, since these dissolve the visual purple out of the retina and therefore impair rod vision. (c) As a symptom of insufficient food. (d) In disease of the retina or chorioid (*e.g.* retinitis pigmentosa). In the last two cases it is usual to find colour vision affected to some extent.

The symptoms of night blindness are well described by the name. The eye does not possess the power of becoming fully dark adapted, and even a moderate degree is only attained after a prolonged stay in the dark. A photochromatic interval is not found, that is to say, when the intensity

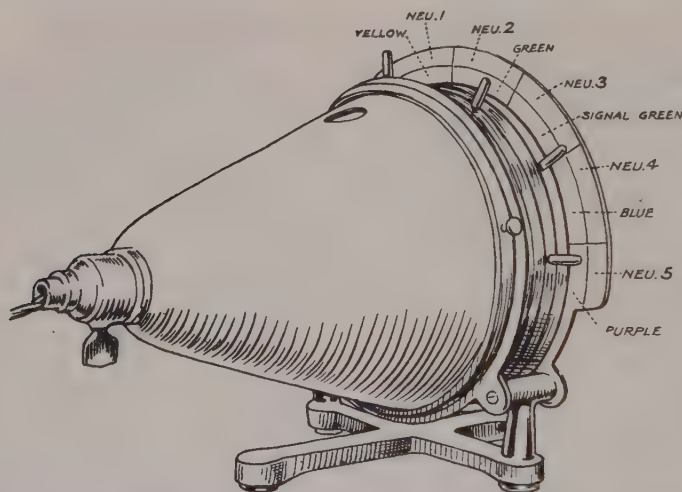


FIG. 260. The Lantern used in practice for the Detection of Colour Blindness. (EDRIDGE GREEN.)

of a colour is reduced, it does not pass through an uncoloured stage (due to the rods). Purkinje's phenomenon is usually poorly developed or is not seen at all. There is no cure in the congenital cases.

COLOUR BLINDNESS. The detection of this condition is important because of the use of coloured signals in the railway and marine services. The employees of such services should be tested at frequent stated intervals, because colour blindness may develop (*e.g.* from tobacco or alcohol poisoning) in a relatively short space of time.

The methods of testing colour blindness fall roughly into three classes: (1) those of historic interest; (2) those used by ophthalmologists for practical tests; (3) those used for research. Holmgren's wool test is an example of the first class. It consists of a large series of coloured worsteds, the number of different shades being very great. In using the test the doctor hands to the patient selected skeins which have been found by experience to give difficulty to colour blind persons. He then instructs the patient to select from the box all the skeins that appear to him to have the same colour. His visual defect is judged by the mistakes which he makes. Since coloured

wools readily fade and get dirty in use, slips of coloured glass or beads, &c., have been used in a similar way. These tests are however no longer employed, because it is found that colour blind persons may be able to pass them without detection.

Of practical methods the lantern test would appear to yield the best results, because it gives a close imitation of a signal light as seen at different distances and under various atmospheric conditions. In using the test, the doctor shows the patient in turn a series of different coloured lights, and in each case asks him to state what he sees. If he makes no mistakes, the colours are shown through modifying glasses which give the effect of a signal when seen through mist, fog, rain, &c., and the answers noted. One definitely wrong answer should reject the patient, particularly if red, green or white be one of the signals misnamed. Objections have been raised to this test, because it is possible for a man ignorant of colour names 'to be failed' even if he has normal colour vision. The objection is readily met, however. When the driver of a train sees a signal, he says to himself "that is a green signal and therefore my train may proceed." But supposing all the time it were a red signal, and that he called it green through ignorance of the name, that man is as much a danger to the community as if he were in fact colour blind. No test can be too searching, and no borderline case should ever be passed; the risk is too serious.

Of tests of theoretical importance some have already been described, namely the measurement of the thresholds for light and colour, the colour-mixing apparatus and the flicker method of photometry. There is, however, another test which is found to give valuable information, namely the spectroscope test of Edridge Green. The instrument consists of a spectroscope to which is fitted two shutters, one of which may be caused to shut off the spectrum from the red end and the other from the violet. The patient commences the test by placing the shutter on the red side at the place where he sees the red begin, and this position on the wavelength scale of the shutter is noted. The patient is then told to move the other shutter until it reaches the place where red changes to orange. This wavelength also is noted. The red side shutter is now moved until it occupies the position of the violet side shutter, and the violet side shutter is now moved until a difference in colour at the two sides of the spectral area, which is thus isolated, is just not able to be seen. The wavelengths are again noted, and the next area measured off, and so on until the violet end of the spectrum is reached. A person with normal vision will with this instrument map out between 20 and 30 distinct strips. Abnormal vision may be shown in three ways: firstly, by the ends of the spectrum being found in abnormal positions, the spectrum being shortened at the red or the violet, or both; secondly, by the isolated strips being too large and too few; and thirdly, by wrong names being applied to some of them. The value of the method is considerable because it shows the presence of all three classes of defect, those due to blindness, those caused by ignorance of colour names, and those in which the appreciation of colour is deficient.

Cases of colour blindness, when tested by the above methods, are found to show every possible variation between complete blindness and slight impairment of the colour sense. Their classification is as a rule complicated by the fact that cases are usually described in terms of one of the theories of colour vision. Most varieties of colour blindness are inherited, and are commoner in men than in women. But it may also be acquired, as explained above, in poisoning by alcohol and tobacco. Cases of colour blindness may be grouped as follows:—

(1) Cases in which the cone mechanism of the retina is not functioning. The patient is found to be colour and day blind; red is not seen at all, while the other colours are seen as different shades of grey. Vision at night is good, vision by day is complicated by the fact that the patient must not expose his eyes to a bright light, for otherwise his visual purple will become

bleached and his rod apparatus therefore cease to function. Owing to the absence of rods from the fovea, this part of the retina is blind. Visual acuity is therefore low. When tested by the flicker method, his luminosity curve is found to correspond with that of twilight vision. His condition may be improved by using neutral tinted glasses fitted with a sky shade.

(2) Cases in which the cone apparatus is apparently normal, that is to say, there is no avoidance on the part of the patient of strong light, no diminished visual acuity, no foveal blindness and no inability to see red light. Yet there is absolute inability to recognise all colours, any one part of the spectrum being able to be matched by any other. Tests by means of the flicker method show a luminosity curve which corresponds to that of day vision. It would seem clear that the retinal apparatus is in every way normal; one is therefore forced to the conclusion that the defect concerns the brain centre which subserves the appreciation of colour. This view is supported by the fact that, between this extreme type and normal colour perception, there are a large number of cases which show various grades of defect. Some, for example, see two colours at the ends of the spectrum only, the intermediate portion being a neutral colour; others see three only, at red, green and blue, and so on. Since in all these cases the cones are apparently normal, they would appear to be a parallel with cases in which there is no trace of deafness, and yet there is an inability to appreciate harmony, or to tell when two notes are in tune. In both types of cases, it would seem that the higher centres of perception and appreciation are either absent or are undeveloped. As might be anticipated, therefore, instruction and practice at colour naming and colour matching benefit a certain number of these cases, so that it is sometimes found that after such instruction the less abnormal cases are not readily detected. If, however, they are tested in a poor light, they are found to make mistakes which a person with normal vision would not commit. As these are the circumstances under which signals have frequently to be recognised, it is for this reason that the lantern test with its modifying glasses is so valuable.

(3) Cases in which certain parts of the spectrum are not seen at all. This condition frequently affects the red end of the spectrum, but it may be found in other parts. The principal effects to be noted are: (1) an abnormal type of luminosity curve, as examined by means of the flicker method; (2) the requirement of different amounts of the primary colours in order to match a given spectral colour, as compared with individuals of normal vision; (3) inability to recognise the normal number of different hues in the part of the spectrum affected, as shown by the spectroscopy test; (4) shortening of the spectrum, if either of the ends of the spectrum is affected. The condition would appear to be directly traceable to abnormality in the colour receiving apparatus of which the cones form an important part. These cases therefore show quite distinct features, which at once differentiate them from those of class 2. A typical example of a case belonging to class 3 will now be described, namely that in which there is shortening at the red end of the spectrum. The flicker test shows that the luminosity curve for different parts of the spectrum has its maximum in the green, instead of in the yellow. Further, the curve does not extend so far into the red, or show such high values in the orange as the normal curve. This curve therefore explains the apparent shortening of the spectrum. Colour mixture experiments show that the patient can match mixtures of green and blue with white light. When required to match yellow, he uses an excessive amount of red, and correspondingly less green than the normal sighted; this test again shows the deficiency of the red

sensation. Tested by the spectroscope, it is found that, besides the shortening at the red end of the spectrum, there is also an inability to distinguish the normal number of hues at the green and yellow. This effect is readily explained, because the difference between green and yellow shades largely depends on the varying extent to which they stimulate the red sensation. When the red sensation is absent, it is clear that the differentiation of greens and yellows must suffer.

EFFECT OF INTENSITY ON COLOUR VISION. It is well known that there is a certain range of intensity over which the appreciation of colour is at a maximum, and that at high and low intensities appreciation is diminished. Thus at low intensity the spectrum will appear shortened at both red and violet ends, and with the spectroscope test perhaps 10 monochromatic areas will be mapped out instead of the normal 20 to 30. At high intensity, on the other hand, the spectrum appears to extend further than usual at both red and violet ends, but again it is found that the number of apparently monochromatic areas is considerably reduced. In the one case it would seem that the impulses received by the brain from the cone mechanism are so feeble that appreciation is diminished, and in the second that a powerful colour stimulus arouses all three sensations indifferently and therefore makes the differentiation of colour difficult.

PERIPHERAL VISION. Experiments with the perimeter show that there is under ordinary circumstances a reduced appreciation of colour in the periphery of the retina. Thus in an annular zone round the macular region there is red-green blindness but full appreciation of yellow and blue. Outside this area coloured objects are seen in different shades of grey. More careful experiments show firstly, that there is no hard and fast line limiting the zones, but a gradual diminution of colour perception on passing in any direction from the centre to the periphery; and secondly, that intensity plays a most important part, an increase being sufficient to effect normal colour perception, even in quite peripheral vision. The red-green blindness found at one intensity might be due either to an absence, or more probably to a weakness or deficiency, of either the red or the green sensations, or to defective appreciation on the part of the higher centres in the brain. In the first case there would be an abnormal shape to the luminosity curve, such as is found in fact in red or green blindness, whereas in the second case the luminosity curve would be similar to that of normal vision. Experiments are said to show that the curve is normal, and therefore the cones in the periphery must be in every way normal, a supposition which is borne out by the correct appreciation of colour at high intensity. Why then, it may be asked, is colour vision reduced at the periphery if the cones are normal? The answer is, probably, firstly, that the number of cones is greatly diminished, and secondly, that the effective area of the pupil is much less at the periphery than it is at the centre of the retina. We have seen in Section I that the threshold necessary for the appreciation of colour depends on the size of the area of the retina which is receiving stimulation. The larger the area the lower can the intensity be. Therefore one unit of intensity falling on 100 cones is equivalent to 100 units falling on one cone. Now consider the relative conditions at the fovea and the periphery; at the fovea let us suppose there to be 100 units of intensity falling on 100 cones, then at the periphery there will be but 50 units (because the effective area of the pupil is less owing to the rays entering obliquely), and these will fall on perhaps two cones only. Whereas in the first case there are 10,000 cone units, in the second there are 100 cone units only, and it is therefore to be expected that appreciation of colour would be decreased, in the same way as it is at the fovea

under reduced illumination.* That blue is perceived at a greater angle than yellow is probably due to the greater refraction of blue than yellow rays when they strike the eye surfaces obliquely. For a blue ray and a yellow ray to meet on the retina, the angle subtended by the blue must be 5 per cent. larger than that of the yellow.

11.—THEORIES OF COLOUR VISION

The value of a theory to science is as much due to the fresh lines of research which it indicates, as to the explanation which it offers of the already ascertained facts. The theories of vision, therefore, are of value in spite of the fact that they do not at the present time offer a complete account of the retina and its functions.

THE DUPLEX THEORY of von Kries states that there are in the retina two entirely separate mechanisms, namely that used for twilight vision, which is colour blind, and that used for day vision, which responds to colour. The view that the rods with the visual purple supply the former, whereas the cones provide the latter, is already familiar, because it has been made the basis of the description given in previous sections. The evidence on which this opinion is based may with advantage be repeated because of its importance.

Twilight vision is found in those parts of the retina where there are rods; it is not present, therefore, at the fovea centralis, which consists entirely of cones. If a spectrum be examined, it is found that the colour with the greatest luminosity is the green, but that red rays are not seen at all. The form of the luminosity curve is identical with the bleaching curve of visual purple, and this pigment occurs only where there are rods. The visual acuity of twilight vision is low, and is explained by the fact that many rods as a rule send their impulses through one and the same nerve fibre. In addition to this experimental evidence, there is the statement that animals (*e.g.* bats and hedgehogs) and birds (*e.g.* owls) which are nocturnal in habit, have rods in their retinae, but not cones.

Day vision is most highly developed in the fovea, from which rods are absent. Not only are the cones at the fovea placed very closely together, but it would appear that each cone connects to one nerve fibre only; in this way the high visual acuity is explained. Further it is stated that animals (*e.g.* tortoises) and birds (*e.g.* hens) which are diurnal in habit have cones only in their retinae.

It has been suggested recently that the following modifications should be made in the duplicity theory of von Kries:—

1. That the cones do, in certain cases, function to some extent in night vision, thus retaining one of the primitive characteristics of rods, from which on morphological grounds they appear to have been developed.
2. That the fovea contains some visual purple, this being necessary in order that the cones may function in night vision as above, or possibly for the green sensation of vision.
3. That the rods play some part in day vision, adding their response to that of the day cones.

These modifications of the duplicity theory concern detail more than they do the basis of the theory, and do not appear to detract at all from the strength of its position. Hence, so far as the relative rôles of the rods and cones are concerned, there would not appear to be any room for speculation. Such is not the case, however, with regard to colour vision because, of the various hypotheses that have been so far advanced, none have been found to offer a feasible explanation of all the known facts, or to leave no other possible alternative. A brief account of the rival theories may with advantage be given.

YOUNG'S HYPOTHESIS states that there are in the retina three different types of cone, each being so made as to respond to one of the three fundamental colours, namely red, green and violet. The impulses from these cones are so combined in the brain that they give a complete picture of the separate coloured images. When all three types of cone are equally stimulated, a colourless sensation results. Each visual unit may therefore be regarded as consisting of three cones, one of which responds to each of the fundamental colours. From this we should expect that the limit to the acuteness of vision would be reached when the separation of the images on the retina is not less than the diameter of such a unit. But the diameter of the foveal cones is

* The above explanation does not, however, adequately account for the fact that peripheral vision does not lose its colour appreciation for blue and yellow so readily as it does that for red and green. The phenomena of peripheral vision still require further investigation.

approximately 0.0025 mm., and therefore that of a unit would be roughly 0.004 mm. Now it is found by experiment that the limit to the acuteness of vision is reached when the retinal images are separated by about 0.002. It is therefore clear that the unit cannot be larger than one cone, and that as a result each cone must be capable of responding to all three fundamental colours. In consequence of this, Helmholtz made the suggestion that there are three different chemical substances, each of which undergoes alteration under the influence of one of the three fundamental colours. The breakdown products thus formed stimulate the cones in proportion to the amount in which they are present, their function in this respect being comparable to the taste buds of the tongue. In this way, each cone can respond to all three colours, and also to white light, and therefore the requirements of visual acuity are satisfied. As to what these chemical substances are, we at present know nothing; it has been suggested that the substance responsible for the perception of blue is a pigment discovered by Kühne, called visual yellow, and visual purple might from its absorption curve provide the pigment for the green, but at present we have no evidence for this. It should be noted that the three sensations are brighter and more saturated than the three fundamental colours with which they may be said to correspond. This follows from the researches

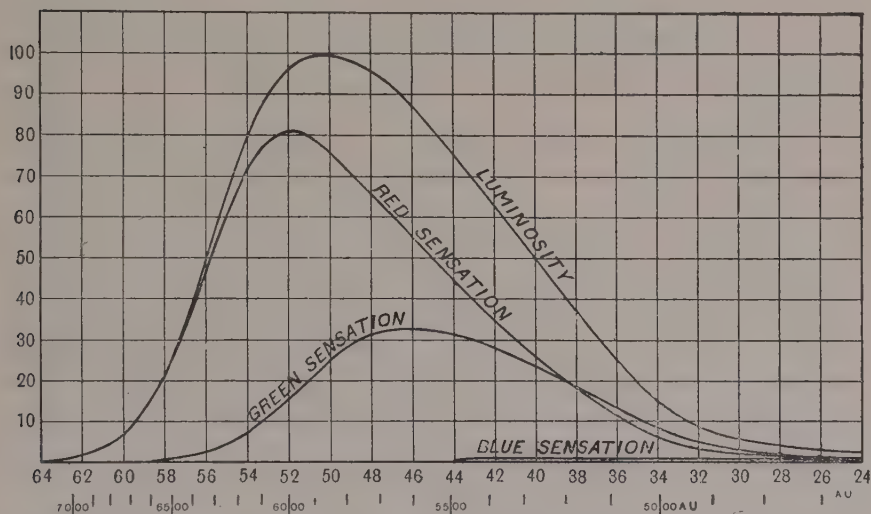


FIG. 261. The red, green and blue Sensation Curves and the Luminosity Curve of white light. Luminosity vertical, wavelengths horizontal. (ABNEY.)

of Maxwell and Abney, which showed that each of the fundamental colours stimulates to some extent the other sensations beside its own. Thus blue light stimulates the green and red sensations to a certain extent, green similarly the red and blue sensations, but red the green slightly, and the blue not at all. This view as to the greater saturation of the sensations finds some confirmatory evidence from the increase which the saturation of a colour undergoes after the eye has been stimulated by its complementary.

Having thus briefly outlined the hypothesis of Young and Helmholtz, their relation-ship with the results of experiment may receive consideration.

1. The results of colour mixture are all adequately explained. Since to each of the fundamental colours there is a corresponding sensation, and since mixtures of the fundamentals can produce the whole range of colour, it follows that corresponding stimulation of the sensations and their resynthesis in the brain fits in with the facts.

2. The various classes of colour blindness which show abnormal types of luminosity curve, abnormal colour mixture values, and possibly also a shortening of the spectrum, are readily explained by supposing one of the sensations to be defective or absent. For example, cases which show a shortening of the red end of the spectrum are stated by the theory to have a deficient red sensation. The luminosity curve calculated on this basis is found to fit closely the curve found by experiment in these cases of colour blindness. The hypothesis would appear, therefore, to be able fully to explain the various cases which fall in this class.

Certain objections have, however, been advanced which it would be well to examine.

(a) That it does not explain why the red blind and the green blind state that the ends of the spectrum, as they see them, are yellow and blue, whereas it would be expected that they would say green and blue if red blind, and red and blue if green blind. An explanation of this behaviour can be readily obtained by examining the forms of the red and green sensation curves, Fig. 261, for in both red and green blindness a yellow light is that which stimulates the remaining sensation most strongly, without at the same time involving the blue. In both types of case, therefore, both red and green are regarded as being but degraded yellows, and the spectrum is therefore named accordingly. (b) That the hypothesis does not explain why these same cases call white white, instead of bluish-green or purple. This is explained by the fact that a colour blind person will call white what his fellows who have normal colour vision call white, because he has learned his colour names from them. In the same way a green blind person will not call the leaves of a tree by a wrong colour, although he will readily err if a piece of paper of the same colour as a leaf be handed to him.

The various types of colour blindness which have normal luminosity curves cannot be explained by the hypothesis without some further elaboration. As indicated, however, they fit in well with the supposition that it is not the eye, but the higher centres which are at fault. The impulses which travel up the optic nerve are in every way normal; the error occurs in their interpretation. This would appear to be a reasonable explanation which agrees with the other postulates of the hypothesis. It has been advanced by Edridge Green as part of another hypothesis of colour vision, which will be given later.

3. Contrast, after images and allied phenomena were not adequately dealt with. Helmholtz regarded contrast as an error of judgment, but Hering showed conclusively that such could not be the case. McDougall's hypothesis, which is to a large extent based on that of Young, will be found to add the features that are required for the explanation of after images and contrast. This theory has recently received valuable confirmation at the hands of Allen. An account of his experiments will be found on p. 334.

HERING'S HYPOTHESIS states that there are in the retina three substances which are always time tending to dissociate into their components. They are, however, either replaced or built up again from substances in the blood as quickly as they are destroyed. There is thus equilibrium between anabolism and catabolism when the eye is unstimulated, and while this is the case no nerve impulses travel to the brain. Now each of these substances is dissociated by one of the following colours, red, yellow, white; and is built up when green, blue or black fall on the retina. Thus one substance will break up when red light falls on it, and will recombine when green does. There is thus a red-green, a yellow-blue, and a white-black substance. When a coloured light falls on the retina these three substances are broken down, or are built up, in varying amounts and corresponding impressions sent to the brain. Tested by experiment this view is found to acquit itself as follows:—

(1) The results of colour mixture are readily explained, with the possible exception of the formation of grey, by the simultaneous anabolism and catabolism of one and the same substance.

(2) Contrast, after images and adaptation are readily explained as follows:—While a stimulus falls on the retina, the three visual substances which were previously in equilibrium with their breakdown products, are caused to take up a new position of equilibrium. On cessation of the stimulus, however, there is a return to the old position, and therefore the impulses sent to the brain are those which correspond to a sensation of an opposite character, thus causing a negative after image. Contrast is explained by supposing that anabolism in one area is accompanied by a stimulus to catabolism in the same area. The effect is not sharply limited, but tends to spread for a short distance over surrounding areas, and thus causes a change in their equilibrium point which is of an opposite nature to that of the stimulus which originates them. Thus blue light falling on a part of the retina causes anabolism in that area, which is followed by an increased tendency to catabolism. This process affects the surrounding area, producing the same change and therefore the same sensation as would a yellow image. Adaptation is explained as the taking up of a new equilibrium point, for one or all of the three substances.

(3) Colour blindness is explained as follows:—Total colour blindness by the presence of the black-white substances only; red-green blindness by the deficiency of this substance, and yellow-blue blindness in a similar way. But we find by experiment that there are two classes of red-green blindness: those which are red deficient, and those which are green deficient. The Hering hypothesis in its present form is incapable of explaining their causation.

EDRIDGE GREEN'S HYPOTHESIS states that the function of the rods is to secrete visual purple. This pigment, under the action of light, stimulates the ends of the cones, and causes them to send impulses to the brain which vary according to the wavelength of the light and its intensity. The rods are, on this view, merely secretory organs, and take no other part in vision. The impulses, having reached the brain, go first to a light perceiving centre, and then to another especially developed for the appreciation of colour. In this colour centre there are three separate mechanisms, which correspond roughly with the red, green and blue fundamental colours, but which may respond to other frequencies than those to which they approximately correspond. Suppose, for example, that a monochromatic yellow light is falling on the retina; it is absorbed by the visual purple and thus stimulates the ends of the cones. These then send up the optic nerve impulses which have a mean frequency corresponding to yellow light, but at the same time contain impulses of other frequencies on either side, to a degree which depends on their closeness with the mean. For example, in the above case, beside impulses of the frequency of yellow light, there are also some which correspond to green and red. These impulses, having reached the colour centre, stimulate the red and green mechanisms respectively, while those corresponding to the yellow also stimulate these same mechanisms, but in proportion to the energy which each receives. This view may now be examined in the light of experiment.

(1) The results of colour mixture would appear to be explained by it, with the exception that the mechanisms in the colour centre must have very definite mean frequencies, for otherwise mixed colours will not be able to match the whole of the spectral range.

(2) Colour blindness was initially explained as being due to defective appreciation in the colour perceiving centre. The shortening of the red end of the spectrum would be due, not to the inability of the retina to react to the stimulus, but to fault on the part of the colour centre when receiving the nerve impulses. A different explanation has been offered by Houston, who has recently elaborated the hypothesis. He states that colour blindness is due to the excessive reaction on the part of the retinal apparatus, which causes the energy of the stimulus to be spread over too wide a range of frequencies. If such were the case, one would expect a low appreciation of colour, as is found in a number of examples of colour blindness, but there would be difficulty in finding an explanation of those cases which show an inability to respond to a part of the spectrum. Although there does not seem to be any special difficulty in so modifying this hypothesis that it fits in with all the varieties of colour blindness, yet it would seem that this would cause it only to be more and more like the theory of Young; but with this important difference that, whereas according to Young's theory the three substances (by which light is selectively absorbed according as its wavelength corresponds to the red, green or blue part of the spectrum), are in the retina, the three mechanisms required by Edridge Green are in the brain. Changing their situation would not appear to have added to our knowledge of them, but would on the other hand appear greatly to enhance our difficulties, for it is impossible to understand how impulses of the enormous frequency of light waves could be transmitted intact up the optic nerves, as Edridge Green's theory requires.

MCDUGALL'S HYPOTHESIS is not antagonistic to Young's theory, as the two previous views have been, but adds valuable suggestions as to the causation of contrast and after image phenomena, points to which the original theory gave little or no attention. McDougall also accepts the duplicity theory. He commences by stating that there are four centres for the two eyes, namely red, green, blue and white (the mechanism of which is the rods), and that these centres are distinct and have no anatomical identity. Between these centres there is antagonism, the red centre of one eye against the green and blue centres of the other and also to a less extent against those of itself. In this way one can explain not only binocular, but also monocular rivalry. Contrast is interpreted in a somewhat similar manner; thus, if the object looked at consists of a red area on a grey field, the red stimulus inhibits the appreciation of red in the surrounding field, and therefore causes it to have a blue-green colour, a deduction which is confirmed by experiment. After images are dealt with in a somewhat similar manner.

With the evidence that has accumulated up to the present before us, there appears to be more in favour of Young's hypothesis than is to be found for its rivals. Further than that, it is not at present advisable to go.

12.—BINOCULAR VISION

Binocular vision may be defined as the co-ordinated employment of two separate visual organs in order to produce a single mental

impression. The advantages of binocular as opposed to monocular vision are :—

(1) Optical defects of one eye are less important, since they are masked by the well-defined images of the other eye.

(2) Defective vision in parts of the visual fields of both eyes is hidden, so long as the defects do not affect the same parts of both fields. Thus under ordinary circumstances, each blind spot does not obtrude itself because in the other eye the image of the same part of the field falls on functional retina.

(3) The combined fields of the two eyes are larger than either alone because, while the features restrict the nasal halves of the fields of both eyes, the combined field contains the unrestricted temporal areas of both retinæ.

(4) Binocular vision under certain circumstances provides a very accurate perception of depth, size and distance, which is called stereoscopic vision.

In order that there should be binocular vision the following conditions should be complied with :—

(1) The fields of the two eyes must overlap. Animals in which the eye axes are parallel have the greatest overlap, and therefore possess the completest binocular vision.

(2) Approximately similar images must be formed on the retinæ, because if this condition is not satisfied, antagonism between the images will occur, as described above, and first one image and then the other will be presented to consciousness.

(3) The retinæ must possess physiologically corresponding points, in order that similar images formed on them may produce one conscious impression.

(4) The external eye muscles must so adjust the visual axes, that the centres of the fields of the two eyes coincide with the images of one and the same object. This adjustment is called fixation. It is sometimes described as the intersection of the visual axes at the point fixated.

(5) The oblique muscles must rotate the eyes about their axes, until corresponding retinal points occupy corresponding meridians.

The rotation adjustment is necessary because otherwise identical points of the retinæ might not correspond, even when the centres did, so that one image would appear tilted at an angle with the other.

FIXATION is partly a voluntary act and partly a reflex process. The former is shown by the fact that the eyes may be directed towards an imaginary object at short distance from the face, so that the eye axes are strongly converging and the accommodation correctly adjusted to the same plane. The presence of a reflex phase is well shown by the fact that no effort of the will is required to sustain fixation on an object in which we are interested, and also by those cases in which when once an object has been fixated, there is found to be considerable mental difficulty in turning the gaze elsewhere. Rotation fixation, on the other hand, appears to be entirely reflex. In order that fixation should be obtained when the gaze is directed in different directions, it is necessary that there should be close association between the corresponding muscles of the two eyes. This is at all events assisted by the anatomical arrangement of the 3rd, 4th and 6th cranial nerve nuclei which has been described previously (see page 297). Not only are the corresponding nuclei on the two sides connected by transverse fibres, so that either the superior recti or the inferior recti move together, but the external rectus nucleus of one side is joined to the internal rectus nucleus of the other by the dorsal longitudinal bundle, so that the eyes deviate together to right and left. Similar connections are to be found between the nuclei of the superior and inferior obliques. The relations of these

nuclei to the cerebral cortex have been ascertained by electrical stimulation. It has been found that stimulation of the median third of the limb of the angular gyrus on either side causes both eyes to be turned to the opposite side. The right gyrus therefore connects with the nuclei of the right internal rectus (3rd) and the left external rectus (6th). Since both these nuclei are on the left, the fibres from the gyri must cross in order to reach their corresponding nuclei: this they do at the level of the superior corpora quadrigemina. The angular gyri are connected to both the frontal and occipital parts of the cortex, so that voluntary movements of the eyes, and also movements under the action of light, can be carried out. Experimental stimulation of the semicircular canals is found to cause conjugate deviations of the eyes. But stimulation of the canals is effected naturally by a rotation of the head, as has been described. The conjugate deviation of the eyes would appear to be initiated in order that the gaze might remain stationary on external objects in spite of the head movements.

THE FIXATION REFLEX.—The way in which involuntary fixation is brought about may be described as follows:—When an image falls on the periphery of the retina, an impulse reaches the oculo-motor nuclei in the manner described above. Thus, suppose the image to come from the right, it will fall initially on the left halves of both retinæ, and impulses will therefore travel to the left calcarine cortex. From here, they will pass to the right-hand centres, causing impulses to travel to the left internal and the right external recti. Both eyes are therefore directed to the right, the movement being such as to bring the image on to the fovea. But as the fovea is approached the impression sent to consciousness becomes increasingly distinct, owing to the higher acuity of the fovea. If the fovea is passed, the image begins to become indistinct again, and therefore the movement of the eyes is checked as soon as the image has reached the fovea. (See also page 300.) If the acuity of the fovea is reduced by disease or by working in a bad light, the definition of the image does not sharply improve as the fovea is reached, and therefore the movement of the eyes is not checked until the image has reached the periphery again. But here the degradation of the image calls for the reverse process, which again causes the image to pass over the fovea. Repeated oscillations of the eyes therefore occur, which are called *nystagmus*. The condition is met with in the day blind, since cone vision is defective in persons whose visual acuity has been lowered by working in a dull light, *e.g.* miners, and in cases of poisoning by tobacco and alcohol.

THE HOROPTER. Theory shows that, even when fixation is properly effected, so that corresponding retinal points occupy the same meridians, images formed on the retinæ do not necessarily fall on corresponding points. For this to be the case, it is necessary also that the objects from which those images are formed should occupy certain definite positions in relationship with one another. For example, if an object 10 feet from the eye is fixated, the images of other objects on either side will fall only on corresponding points if these lie on a circle of 5 feet radius, the centre of which is between the observer and the object fixated. For calculation shows that only then are the images formed on the two retinæ the same distance from the centre. The form of the curve, which is called the horopter, is found to change with the different directions of the gaze. When the gaze is directed to a point on the floor, it is stated that the horopter almost corresponds with the plane of the floor.

MONOCULAR DEPTH PERCEPTION. The perception of depth with the single eye is found to depend on a number of different factors, which as a rule operate together:—

(1) The apparent size of objects, the dimensions of which are known. Thus the size of a man being approximately known, his distance away is

deduced from the size of the image which is formed on the retina. The further away he is, the smaller his image will appear.

(2) The colour of an object being known, the effect of distance in modifying that colour is used in depth perception. Thus trees, which when near look yellow-green, when seen at a distance through an intervening layer of haze appear blue-green or even blue. This fact is made use of by artists for expressing distance.

(3) The partial obstruction of a distant plane by objects nearer to the observer.

(4) The shadows which one plane casts upon another.

(5) The intensity of the light which is reflected by the object frequently varies with its shape and position. For example, the shape of a solid sphere can be accurately inferred from the distribution of intensity over its face.

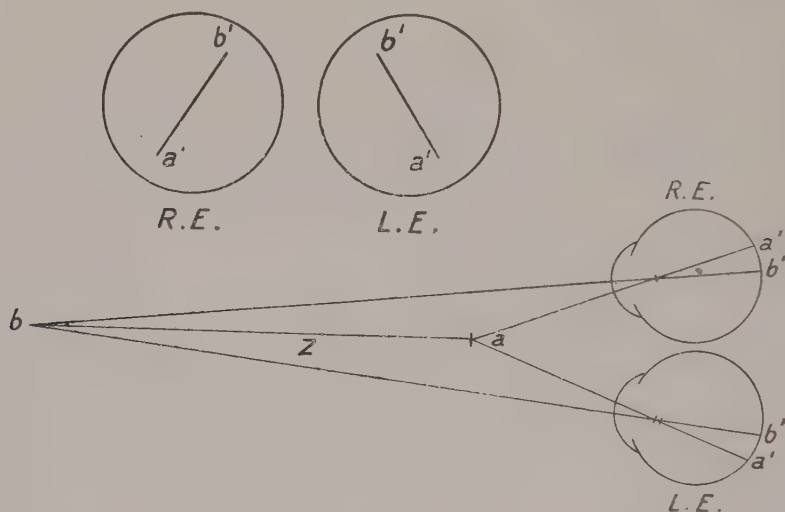


FIG. 262. The eyes are directed to the point *b*. A thread hung obliquely at *a* gives rise under these circumstances to the images shown in the upper figures —i.e. two images which do not lie on corresponding points. Nevertheless the thread is seen as single.

(6) By perspective, which may be defined as the geometrical arrangement of lines in the image formed on the retina. Thus the lines of a tennis court seen diagonally from one side are all found to converge to one or other of two points on the horizon.

(7) By the intersection of objects with the horizontal plane. Thus the positions of trees in a field may be inferred with some accuracy, if the positions of the roots of the trees in relationship with the boundaries of the field be observed.

(8) By parallax, that is, the rate of movement of objects in relationship with one another. Thus if a middle plane be looked at, it will be noticed that objects in a plane behind appear to move in the same direction as the observer, while those in a plane in front appear to move the opposite way. Even when we are standing still, we are all the time making involuntary movements which cause the development of parallax. This process is probably one of the most important in producing the monocular effect of depth.

(9) By the effort of accommodation required to focus an object sharply.

In man the accommodation is found by experiment to give little or no perception of depth, possibly because the function is involuntary. It is thought that in birds, in which the ciliary muscles are striated and are under voluntary control, the accommodation may give valuable information of distance.

All the above factors operate together to produce an appreciation of distance which as a result of experience reaches a very high order, and with the exception of the last two, are used by the artist to produce the effect of solidity and reality. Any good picture shows us that the result can be very convincing.

STEREOSCOPIC VISION is the binocular perception of depth. It consists of all the factors which operate in the case of each eye separately, and in addition uses :—

(1) The convergence of the eye axes which is necessary in order to cause images of near objects to form on the fovea simultaneously.

(2) The dissimilarity between the images which are formed on the two retinae. (Cp. Figs. 262 and 263.)

That convergence has very little effect on the perception of distance can be proved by placing weak prisms, either base in or base out, in front of the eyes and in this way changing the convergence of the eye axes without changing any other condition. It is found that the apparent positions of objects are unaffected.

That there is dissimilarity between the images formed on the retina can easily be proved by experiment. Thus, if the gaze be directed towards a distant point, and the finger be held a short distance from the nose, the finger appears to be to the right of the distant point with the right eye and to the left with the left. If two photographs be taken of the same scene, but with the camera for the second photograph three inches to one side of its position for the first, it is found that, when the two negatives are placed so that objects on the horizon correspond, there is a lateral difference of position in the case of all other objects situated nearer to the camera. Measurement shows that the nearer the object the greater the difference in position. Since this is the case, it is clear that only images in one plane can be formed on corresponding retinal points ; images in all other planes must fall on points which are discrepant. Two questions therefore arise : (1) Do we see such objects doubled ? (2) If we see a single image only, is it because one of the images is displaced from consciousness by the antagonism of the other ?

An answer is given by the following experiment :—A Brewster's stereoscope is taken, the optical arrangement for which is shown in Fig. 264. At B and B' two similar lantern slides are placed which show a view of any distant objects. On looking through the instrument towards the point S, the directions of the rays are changed so that the images of the slides are seen to overlap one another. By shifting one of the slides the images may be made to fall on corresponding points of the retinae, and they then form a single combined picture. In front of these slides is now placed another pair of slides which show the photograph of an index mark. If the indices are adjusted so that

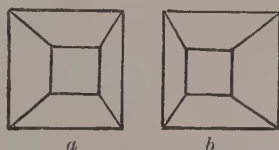


FIG. 263. To show the difference in the Images of a Truncated Pyramid as given by the right and left eyes.

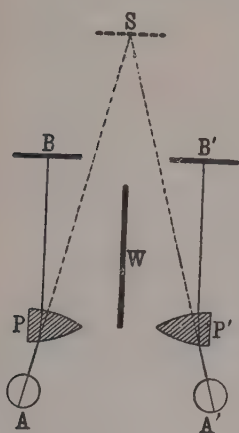


FIG. 264. Brewster's Stereoscope.

they occupy corresponding positions in relationship with the objects on the slides below them, on looking into the instrument it will be seen that these marks appear to lie in the same plane as the distant objects placed on the slides below them. If one of the index marks be moved towards the axis of the instrument, it will be seen on looking into the eyepieces that the indices now appear to lie in a plane considerably in front of their previous position, in fact that the closer they are placed together, the nearer do they appear to the observer. But the indices do not show double images unless they are moved a considerable distance together, and then the effect of distance ceases. If one of the index slides be removed and the other be moved towards and away from the axis of the instrument, the index is not found to shift its plane towards or away from the instrument. This shows that for position to be appreciated both images must be presented to consciousness simultaneously without appearing double.

THE ACUITY OF STEREOSCOPIC VISION has been investigated in such a way that other factors which normally assist distance perception were excluded. Two methods have been used: (1) to adjust the position of a thread which lies between and parallel with two other threads until they all appear at the same distance from the observer; (2) to observe the fall of small coloured bodies of unknown size, and then to state the position of the line of fall in relationship with a fixation mark. The former method at 2 metres distance shows an average error of 1.5 mm., the latter method at the same distance an error of 40 mm. The difference between the results of the two methods is considerable; but it should be noted that in the fall method the object is seen only for 0.02 sec. If in the thread method the threads be placed horizontal it is found that the appreciation of distance is greatly impaired. The greatest acuity is found when the threads are vertical. If however the head is turned so that the line joining the two eyes is vertical, the greatest acuity is found when the threads are horizontal. This would be expected if the appreciation of distance is greatest when the parallax of the objects at the two eyes is greatest. Experiment shows that the recognition of position in relationship with a definite fixation mark is much more accurate than recognition of absolute distance in which there is no point of reference. Thus it is well known how inaccurate the estimation of the distance of a single source of light at night may be.

HYPOTHESES OF DEPTH PERCEPTION. Javal's view was that the movements of the eye muscles, which are necessary in order to direct the gaze from objects in one plane to those in the next, caused impulses to travel to the brain which are interpreted in terms of distance. This view was ruled out by the fact that images which are formed on the retina for a short length of time only (0.02 sec.) can be perceived in relief.

HERING'S HYPOTHESIS was that it is the formation of similar images on points of the retinae that do not correspond which causes distance perception. If the disparation is crossed, the object appears nearer than the fixation mark by an amount which depends on the amount of the disparation. If, on the other hand, the disparation is uncrossed, the object is recognised as being further away. Hering supposed moreover that crossed disparation acts as a stimulus to convergence and accommodation, while uncrossed produces the reverse effect. We may now inquire how this hypothesis fits in with the facts. To commence with, if depth depends on disparation, it is clear that, when we perceive objects lying in different planes, we must subconsciously group them according as they fall on corresponding retinal points, or on points which are discrepant by one, two, three or more cone widths, and whether the discrepancy is crossed or uncrossed. The amount of the discrepancy must be some whole number of cone widths, because it is clearly impossible to stimulate half a cone with one impression and the other half of the same cone with a different one and obtain two distinct sensations. It is clear that space must be divided, so far as stereoscopic vision is concerned, into a number of concentric shells, the centres of which correspond with the position of the observer. Now the thickness of these shells can be readily calculated: at 1 metre they are found to be 2 mm. thick, at 10 metres 200 mm. thick, and at 100 metres 17 metres thick. If we are looking at a fixation mark 10 metres away, objects 100 mm. nearer to and 100 mm. further from the observer will lie in the thickness of one and the same shell, and will therefore appear the same distance from the observer. Objects between 100 and 300 mm. nearer to the observer will lie in the shell corresponding to one cone discrepancy, and will therefore be appreciated as being at a different distance from the observer, appearing nearer if crossed, and further if uncrossed. The same

reasoning applies to objects at other distances. If this calculation is correct, it should be necessary to place objects more than 100 mm. from a fixation mark, which is itself placed at 10 metres, in order that a difference in the distance from the observer should be appreciated. Greeff found by experiment that $\frac{1}{50}$ th the distance of the fixation mark was necessary (i.e. 200 mm.), the observations being instantaneous ones. If time be allowed for prolonged observation, greater accuracy in the appreciation of distance is obtainable, because different points of fixation can be used. Suppose for example that two objects 20 mm. apart be examined at a distance of 10 metres, under instantaneous observation they will appear identical as described above; but if the examination be made more carefully, it will be found that, on fixating a point a mean distance of 100 mm. away from the objects, the distance between the two is suddenly appreciated because the demarcation between two shells now falls between them. It is in this way that the accuracy of extended observation becomes greater than that obtainable with instantaneous. The limit reached by experiment is stated to correspond to a displacement at the retina corresponding to $\frac{1}{10}$ th the diameter of a cone. The corresponding values for the acuity of stereoscopic vision would be $\frac{1}{10}$ th those given above, namely 0.2 mm. at 1 metre, 20 mm. at 10 metres, and 1.7 metres at 100 metres. Hering's view would therefore appear to agree well with the results of experiment. It remains to consider the type of cortical mechanism that would be necessary for the estimation of the discrepancy between the images. One type may be briefly described as follows:—To a number of parallel planes in the left side of the cortex are connected the terminal ends of the nerve fibres from the left halves of the two retinae. At the middle plane fibres from exactly corresponding retinal points are connected together. At planes which lie superficially to the middle plane are connected other terminations from the same fibres but with a crossed lateral discrepancy of one cone in the 1st plane, two cones in the 2nd plane, three cones in the 3rd plane, etc. At planes which lie deep to the middle one other terminations from the same fibres are connected, but with an uncrossed lateral discrepancy of one, two, three, etc., cones as the case may be. On looking at a fixation mark on a uniform background, therefore, a series of impressions of the mark will be formed on all these planes, but in the central one only will they exactly agree, for in all the others the lateral discrepancy will cause the impressions to be duplicated. In all these other planes there will thus be antagonism, first one image and then the other predominating. When these images are combined in consciousness, the stable image from the central plane will suppress the unstable ones from all the other planes, the result being a single picture of the fixation mark. If there are in front of the fixation mark other objects lying in planes at different distances from the observer, the impulses sent up by the cones to the cortical plane will not correspond at the central plane, because their images no longer fall on corresponding points, but they will correspond in the superficial planes where the discrepancy of their images agrees with the discrepancy of the nerve connections. These other planes will therefore predominate according as each contains the identical images, and when they are combined in consciousness these planes will suppress all the others. Since each cortical plane represents a certain lateral discrepancy, it must also represent a certain distance from the fixation mark. If consciousness recognises the plane in which stable image is formed, it also must appreciate the distance of the object lying in that plane from the fixation mark. This would not seem any more difficult than the localisation of a touch on the skin. So far as we are able to judge there is nothing inherently impossible in the arrangement of the hypothetical cortical mechanism which has been outlined above, and therefore Hering's theory would appear to be very plausible.

CHAPTER XXIV

HEARING

1.—PROPERTIES OF SOUND

SOUND is propagated by waves consisting of alternate compressions and rarefactions which travel through the medium. Any medium which has the properties of elasticity and mass can conduct sound; thus solids, liquids and gases are all efficient conductors. Since sound is a form of wave motion it exhibits many of the properties which are found in the case of light, namely Reflection, Refraction, Diffraction, etc. But owing to the long wavelengths of sound waves compared with those of light, the effects of diffraction are relatively of greater importance. Therefore sound does not form sharp shadows, such as light does, and is found to bend round obstacles and to be conducted down speaking tubes, etc., in a way that would be impossible if sound were of shorter wavelength.

SOURCES OF SOUND are so well known to us, that the fundamental property of a source of sound tends to be forgotten, namely that to produce sound, motion has to be initiated in a sound conductor which has a velocity the same or greater than that of the transmission of sound. Thus when a book is closed with a snap, the book becomes a source of sound when the velocity at which the air is squeezed from between its pages is equal to the velocity of sound in air. A stick stirred in water becomes a source when the ripples (eddies) it produces have the necessary velocity to cause a wave motion. Sounds have been divided arbitrarily into two classes, namely tones and noises; the former produce pleasant and the latter unpleasant (harsh, grating, screeching, &c.) sensations. Between the two extremes fall the sounds of everyday life. Thus music as a rule consists of tones, but may be found to consist of chords which examined singly could be grouped as noises. And so at the other end of the scale, when we strike a single stick with a hammer the effect is that of a noise. If, however, we take a series of sticks of different lengths and strike them in succession, it will be noticed that the sound produced by each stick corresponds to a distinct note, and tunes may be played on such a collection of sticks.

SOUND ANALYSIS has been effected in a variety of ways: (1) By the magnification of gramophone and phonograph records. (2) By optically recording the electric vibrations set up in a circuit containing a microphone. (3) By optically recording the excursions of a diaphragm or membrane on which the sounds are caused to fall.

When thus recorded, sound waves are usually found to be of a highly complicated nature. Only when a pure tone source of sound (*e.g.* a weakly sounding tuning fork) is being recorded is the sound wave regular in form. The records of the waves set up by the majority of musical instruments, which appear complicated to the eye on first inspection, can be shown to be analysable into a number of simple sine wave constituents. In the case of noises, such an analysis is not possible, unless a very large number of constituents are assumed to be present.

INTENSITY AND PITCH. In a similar manner, loudness or intensity is found to depend on amplitude (as in the case of light), while pitch depends on the wavelength, short waves having a high, long waves a low pitch. This can be proved in other ways: thus if a violin string be bowed forcibly, the excursion of its string at each vibration is greater than when it is bowed gently, and the amplitude of the corresponding alternating waves of sound varies in proportion to that of the vibrating body by which they are started. By attaching a pointed slip of paper to the end of a tuning-fork and so recording its vibrations on a blackened surface, it is easy to see the connection which exists between the amplitude of vibrations and the loudness of the sound produced by the vibrating fork.

That the pitch of a tone depends on the frequency of the vibrations is shown by means of the syren and the klaxon. As the speed of rotation increases, and therefore also the number of impulses imparted to the air per second, so the note appears to us to be rising. Since sounds of high and low pitch travel with the same speed, the distance between the waves diminishes as the number of impulses per second increases.

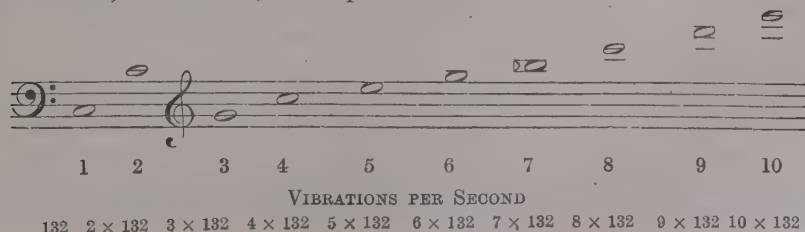
LIMITS OF PITCH. The ear is unable to perceive tones the pitch of which falls above or below certain fairly well-defined limits. If the number of vibrations is less than about

thirty per second no musical tone is produced, the individual vibrations being perceived as a series of pulses in the surrounding air, and it is only when we increase the number to about forty per second that we are able to appreciate a pitch in the note produced. As the number of vibrations per second is increased the note rises steadily without break till we arrive at 15,000 vibrations per second. Above this number of vibrations, the human ear is incapable of perceiving any note at all, though it is probable that small animals can hear notes still higher in the scale. In music neither the lowest nor the highest tones are used. The lowest tone of large organs, that of the sixty-four foot pipe, is 16 vibrations per second, and one can hardly speak of its effect as that of a musical tone. The highest notes employed in music are *a*4 and *c*5 with 3520 and 4224 vibrations per second on the piano, and *d*5 with 4752 vibrations on the piccolo flute. In music therefore we only employ between 40 and 4800 vibrations per second, *i.e.* about seven octaves.

SOUND AUGMENTORS. Experiment shows that the intensity of the tone produced by a sound source can be considerably increased by the use of sound augmentors. These are called resonators, sounding boards or trumpets, according to the form they take or the sound source (musical instrument) to which they are applied. If from any string instrument (*e.g.* violin) the box be removed, the tones generated are found to be greatly reduced in intensity. The function of these sound amplifiers appears to be to transmit the vibrations of the source (*e.g.* the stretched wire) to the greatest possible volume of air, *i.e.* to turn into sound as much of the kinetic energy of the vibrating wire as possible. In the case of the trumpet or horn, there is in addition the effect of increasing the volume of sound in some chosen direction at the expense of that in others. This effect is well illustrated in the gramophone. In most musical instruments the amplifier must be capable of responding to a large range of tones indifferently, and the more perfectly it can do this the better is the instrument. Such perfection is difficult to obtain, and more usually it is found that in spite of all care one note is accentuated more than others, *e.g.* the 'wolf note' of the violin. Sound amplifiers for the reed stops of the organ are, on the contrary, made as sharply selective as possible, in order that of the many tones emitted by the vibrating reed, the chosen one shall alone be augmented. This form of amplifier is called a resonator, although the term is, strictly speaking, applicable to other classes of sound amplifier, *e.g.* the sounding board. This power of augmenting one chosen tone has great value, because in a musical chord it is possible at once to detect the presence of any particular tone, by ascertaining whether its resonator responds when the chord is sounded. For such analysis the resonators of Helmholtz are generally employed. These are hollow vessels open at one end and having a tube at the other to which the ear may be applied. A series of graduated sizes are used, each of which has a definite period of vibration (pitch).

TIMBRE OR QUALITY. When the same note is sounded on different instruments, *i.e.* tuning-fork, violin, piano, trumpet, human voice, every person, whether he has an educated musical ear or not, can say at once what kind of instrument is being used. This fact shows that the sound wave produced by these instruments must differ, altogether apart from any differences in amplitude or in number of vibrations per second; and if the sound waves produced by these instruments be recorded, an actual difference is found in the shape of the curve.

If a stretched wire be plucked so as to set it into transverse vibrations, it will give out a certain note, dependent on its length, its thickness and the tension to which it is subjected. If its length be halved, it will give out a note which is of double the number of vibrations per second. If only one-third of the wire be set into vibrations, the sound wave produced will have three times the number of vibrations of that of the whole string. When the string is free to vibrate as a whole, the segments of it tend to vibrate even while the whole string is vibrating. If, therefore, we take the note given out by the whole string, the 'fundamental tone,' as corresponding to 132 vibrations per second, there will also be a series of notes superadded to the fundamental tone with vibrations per second in the ratio of 1, 2, 3, 4, 5 and 6, etc. Thus if the fundamental tone be *c*, the overtones, or harmonics, will be produced as shown below:



Nearly all musical instruments, as well as the apparatus for producing the human voice, resemble a stretched wire in giving out overtones in addition to the fundamental tones; and the difference in the quality of various instruments is chiefly determined by the varying predominance of the different overtones. In some the higher overtones may be most marked, in others only the lower overtones. The tuning-fork is practically the only instrument the note of which is pure, *i.e.* free from overtones. It must be remembered that these different tones arrive at the external ear simultaneously. We do not have some particles of air vibrating at one rate and other particles at another rate, but all the simple vibrations of which each component tone is composed are combined together to form a compound wave, the shape of which differs according to the constituent vibrations of which it is made up, and to the time relationship (phase) between them.

Thus in the diagram (Fig. 265) the wave shown by the continuous line is compounded of the series of simple vibrations represented by the different dotted lines. The component fundamental overtones and harmonics can be readily identified in a tone experi-

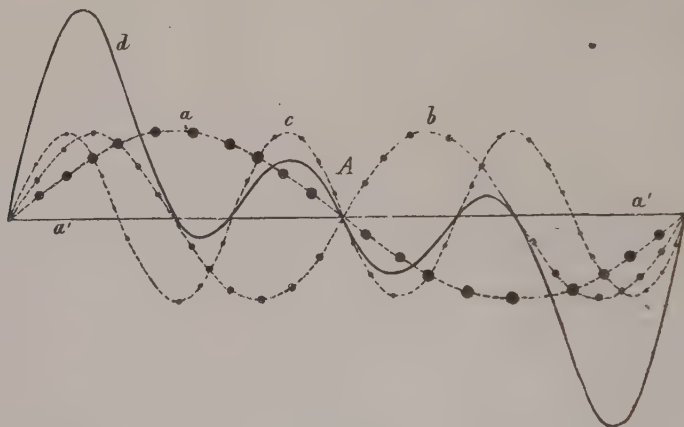


Fig. 265. *d*, a Compound Sound Wave, which may be analysed into *a*, the fundamental tone, and *b* and *c*, the first and second overtones. (HENSEN.)

mentally, by employing the series of resonators described above. By practice it is possible to train the ear to recognise strong overtones without the use of resonators.

THE ORGAN OF HEARING

From a knowledge of the fundamental properties of sound, it is possible to infer the probable features of the organ of hearing. In its simplest variety the organ would take the form of a sounding board or diaphragm, which would be set into vibration by the incident sound waves. The vibrations of this plate would be identified by touch cells similar to those found in the skin, which would be so placed that the diaphragm during its motion should come into contact with them. Such an apparatus would respond to and estimate the total intensity of sound. To identify the pitch a series of resonators would be required, each of which would be sharply tuned to one of a series of tones. Of the many types of resonator that could be employed, a series of stretched wires would appear to be the simplest and most compact. The receiving apparatus would therefore take the form of a harp, with a touch cell and its respective nerve attached in close approximation to every chord.

In order that such a mechanism may be formed of organic material and be kept nourished during life, it is necessary that it be immersed in a liquid similar to that which bathes the eye media. The sound waves must therefore be transmitted from the air to this fluid. In order that this may

occur it is necessary that the sound waves reach the apparatus either (1) through the walls of the chamber containing the apparatus, *i.e.* bone conduction, or (2) through a membrane separating the liquid from the air, or (3) by means of suitable levers which would impart to the liquid the vibration of an external diaphragm. The advantage of the last method would be that the intensity of sound reaching the apparatus could be considerably increased. This desirable result could be still further achieved by concentrating the sound waves on to the diaphragm by means of a trumpet and by

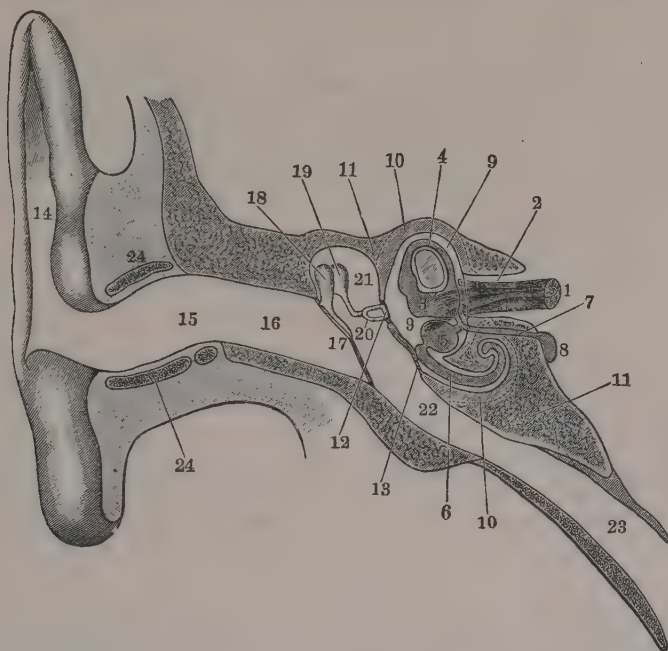


FIG. 266. Diagrammatic View of Auditory Organ. (After SCHAFER.)

- | | |
|------------------------------------|-------------------------------|
| 1. Auditory nerve. | 13. Fenestra rotunda. |
| 2. Internal auditory meatus. | 14. Pinna of external ear. |
| 3. Utricle. | 16. External auditory meatus. |
| 5. Sacculæ. | 17. Membrana tympani. |
| 6. Canalis media of cochlea. | 18. Malleus. |
| 9. Vestibule containing perilymph. | 19. Incus. |
| 12. Stapes. | 23. Eustachian tube. |

causing the trumpet to be adjustable in different directions. The position of the source of sound could then be ascertained.

Such an organ of hearing would therefore consist of three different parts : (1) the horn or trumpet with its adjusting muscles, called the external ear ; (2) the diaphragm and levers for receiving the sound vibrations and for transmitting them to the internal mechanism, called the middle ear ; and (3) the internal mechanism consisting of the resonators, with their respective touch cells and nerves, called the internal ear.

2.—STRUCTURE OF AUDITORY APPARATUS

EXTERNAL EAR

THE EXTERNAL EAR consists of two parts : (1) that external to the skull, called the pinna, and (2) that internal, called the meatus. The pinna *in animals* is a horn-shaped structure which is provided with two sets of muscles. The immediate response to a

slight sound is a pricking of the ears by means of the intrinsic muscles, and the directing of the orifices towards the source of sound, through the action of the extrinsic muscles. The functions of the pinna are firstly to ascertain approximately the direction of the source of sound, and secondly to concentrate the sound waves into the meatus. It may also be said to have a third function, namely to protect the internal structures; the stiff hairs with which it is provided must prevent to a considerable extent the entrance of foreign bodies.

In man the pinna has undergone retrogression; not only has it lost its trumpet shape, but also it has become almost entirely immobilised from disuse. It is improbable, therefore, that in man the pinna has any power of accentuating sound waves; this is borne out by experiments in which the undulations are filled with wax, and by cases in which the pinna has been cut off.

The form of the pinna in man may have a slight influence in the judgment of the direction from which sounds proceed. It has been noticed that a compound tone changes slightly in quality as its position in relation to the ear is altered. This is partly due to the fact that the auricle may reflect a fundamental tone more strongly than the partial, or the converse. According to Rayleigh this difference in quality is determined chiefly by the fact that diffraction of the sound waves occurs as they pass round the head to the ear remote from the source of the sound, so that the partial tones reach the two ears in different degrees of intensity, and determine a difference in quality of the sound as heard by the two ears.

THE EXTERNAL AUDITORY MEATUS in man is about one inch long, and directed forwards, inwards and slightly upwards. Its general function, other than as a mere conductor of the sound waves, is to protect the delicate vibrating *membrana tympani* which closes its inner end. This it does partly because of its narrow tubular shape and partly owing to its considerable curvature. Opening on the skin of the meatus are special sebaceous glands which secrete a yellow wax (*cerumen*) with bitter taste and peculiar odour. The wax not only protects the cuticle of the ear and the *membrana tympani* from drying, but, together with the hairs at the orifice of the meatus, serves to repel insects and to prevent their entering. By the length of the meatus moreover the drum is protected from draughts and its temperature is maintained constant.

In animals the junction between the pinna and meatus is so fashioned that the orifice can be restricted by means of a constrictor muscle. This permits the intensity of sound reaching the internal mechanism of the ear to be controlled, as is light by the iris in the case of the eye.

THE MIDDLE EAR

This consists of a cavity, hollowed out of the temporal bone, which communicates externally with the meatus, internally by two windows, one circular and the other oval, with the series of chambers forming the internal ear, and below by means of a long duct called the Eustachian canal, with the throat. At the junction with the meatus is a special bony ring to which is attached a thin diaphragm, the *membrana tympani* (or drum), which completely closes the orifice.

THE MEMBRANA TYMPANI. The sound waves which pass down the external meatus impinge on the drum of the ear and set this into vibration. The vibrations are thence transmitted by a chain of three small bones, the auditory ossicles, across the cavity of the tympanum to the fluid which bathes the terminations of the auditory nerve in the internal ear. Since the drum of the ear has to pick up and transmit vibrations of every frequency, and to reproduce accurately in its movement the finest variations of pressure in the course of the wave, it is essential that it should be devoid of any periodicity, *i.e.* a tendency to vibrate at a certain frequency. If such periodicity were present, the ear would pick out and magnify, to the exclusion of the other overtones, some particular overtone present in the compound tones reaching the ear. The perfect aperiodicity of the tympanic membrane is secured by its structure and attachments. The membrane is composed of a thin layer of fibrous tissue, covered externally with skin and internally by the mucous membrane of the tympanum. To its inner surface is attached along its whole length the handle of the malleus, the first of the auditory ossicles. This attachment of an elastic membrane to a mass of bone would itself tend to damp any vibrations of the membrane. By the attachment of the tendon of the tensor tympani muscle to the inner surface of the handle of the malleus, the middle of the membrane is drawn inwards, so that it forms a cone whose walls are convex outwards. The membrane is built up of circular and radial fibres, the circular being best marked towards the periphery. By the dragging inwards of its central part it follows that the tension of its constituent fibres varies from point to point, so that each bit of the membrane has a different periodicity and the membrane as a whole is aperiodic.

By exposing the tympanum from above, it is possible with a microscope to observe

the actual movements of the handle of the malleus when sound waves fall on the tympanic membrane. The maximum movements at the apex of the cone may be taken as about 0.04 mm., but sounds are easily audible which would produce movements of the tympanic membrane quite imperceptible under this method of examination.

THE OSSICLES. Stretching across the tympanum, from the *membrana tympani* to the outer wall of the internal ear, is a chain of ossicles, which are named respectively the malleus, the incus, and the stapes (Fig. 267). These ossicles are articulated together, so that a movement inwards of the malleus causes a movement inwards of the base of the stapes. The *malleus*, or hammer bone, consists of a thickened head, from which two processes run, the *manubrium* which is attached to the tympanic membrane, and the *processus gracilis* by which it is anchored to the walls of the tympanic cavity. By means of three ligaments, it is so fixed that it is capable of rotating only around a horizontal axis, which passes through the anterior ligament, the head of the malleus, the body of the incus and the short process of the incus. When the manubrium is pushed inwards, the part of the malleus above this axis must move outwards. The *incus*, sometimes known as the anvil bone, is articulated with both the stapes and the malleus, and a ligament passes from its short process to the posterior wall of the tympanic cavity. The posterior surface of the rounded head of the malleus fits into the saddle-shaped cavity on the anterior surface of the incus, while the tip of the long process of the incus is articulated with the stapes. Movement inwards or outwards of the head of the malleus causes rotation of the incus round an axis which passes from the tip of the short process through its body. Thus when the handle of the malleus moves inwards, the greater part of the body of the incus and of the head of the malleus moves outwards together, while the long process of the incus moves inwards. The *stapes* or stirrup bone is fixed in the fenestra ovalis of the internal ear, in the inner surface of the tympanum, by the annular ligament. It is placed almost at right angles to the long process of the incus, and therefore is pressed into the foramen ovale when this process moves inwards.

THE MUSCLES found in the tympanum are the tensor tympani, which is attached to the handle of the malleus, and the stapedius attached to the base of the stapes. The tensor is innervated by a motor branch of the 5th cranial nerve, and when it is stimulated it draws the handle of the malleus inwards and so increases the tension of the tympanic membrane. At the same time the plunger of the stapes is displaced into the oval window, thus putting compression on the contents of the internal ear. The contraction of the tensor has been supposed to have a protective function and has been compared to the sphincter pupillæ (Helmholtz). Others hold that it modifies the response to low and medium tones, but even here there is a divergence of opinion because, while some hold (probably correctly) that the tensor by its contraction decreases the natural period of the drum and thus enables it to respond to rapid changes of phase and high tones, others have held the opposite view. Observation shows that contraction occurs when sounds (particularly tones of high pitch) fall on the drum, and that the contraction is bilateral, even if the stimulus be only unilateral. The reflex therefore travels via the auditory nerve to the motor centre of the 5th nerve.

Since the tensor tympani is uncontracted when no sounds are falling on the ear, it

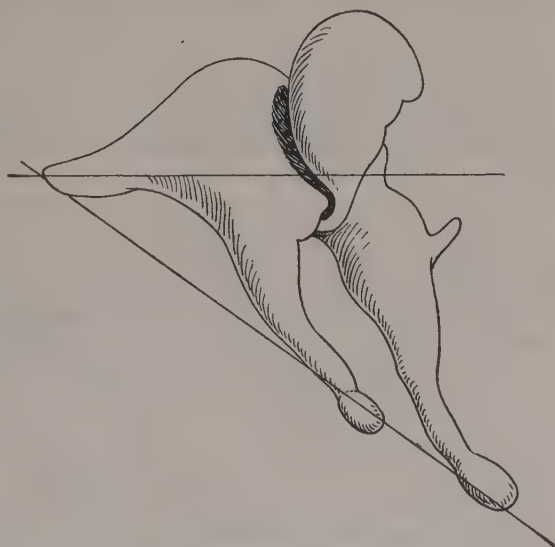


FIG. 267. To show the Relations of the Malleus and Incus to one another.

The shaded area between the two bones shows the articular surfaces which connect them. The overlapping of the two bones at the lower part of these surfaces is well shown. It is this arrangement which causes motion to be conveyed from one to the other.

allows the drum to go slack and therefore tends to prevent this membrane from becoming stretched through being continually in tension.

The stapedius muscle is innervated by a twig from the facial nerve. Its function is problematical. Some say it antagonises the tensor by decreasing the tension on the drum; others that it reduces the tension on the contents of the internal ear by diminishing the pressure of the stapes on the oval window. Hartridge's view is that the function of this muscle is to cause the body of the incus to engage with the spur of the malleus with sufficient force to prevent chattering and lost motion when the vibrations are being transmitted from one bone to the other.

THE EUSTACHIAN CANAL is a tube about 35 mm. in length, which connects the middle ear with the pharynx. Normally it is kept closed in order that the respiratory rhythm may not affect the pressure in the tympanum, and that the noise set up by the flow of air and the voice may not be heard. When the canal is shut, the middle ear becomes a closed chamber, which appears to increase the response to low tones. Since variations in barometric pressure would not be communicated to the middle ear if the canal were always closed, the air pressure on the two sides of the drum would be found to vary. This is avoided by a periodic opening of the canal which accompanies the acts of swallowing and yawning. When the throat is infected, the inflammation often spreads to this canal, which then becomes blocked, either by mucus or by the swelling of its mucous lining. The air in the middle ear is then gradually absorbed and the difference in air pressure on the two sides of the drum decreases its response to sound, and the affected ear thus becomes partially deaf.

Temporary deafness also occurs if the barometric pressure is suddenly altered by a rapid change of level (as in an aeroplane) or by the application of external pressure (as in a caisson or submarine). The deafness is however immediately relieved by swallowing, because the altered pressure is communicated to the other side of the drum through the opening of the Eustachian canal.

FUNCTIONS OF TYMPANUM. The function of the tympanic apparatus (consisting of drum, bones and muscles) is to transform the energy of the aerial vibrations incident on the drum into a series of mechanical movements of the plunger of the stapes, by which the pressure within the internal ear is rapidly varied. The evidence may be summarised as follows. (1) If in man the external ear be made to form a gas chamber which is connected with a manometric flame, the flame shows vibration when sound falls on the drum, which could only be caused if the drum were set into vibration. (2) If the drum be gilded, and a beam of light be made to fall on it, the excursions of the beam caused by vibrations of the drum can be recorded photographically, and are found to accompany the incidence of sound waves. (3) If to the chain of ossicles a light writing lever be attached, the point of which travels over a rotating smoked drum, when sounds fall on the drum the vibrations are recorded, showing that the ossicles are set into movement. (4) By opening the middle ear from above, and sprinkling the ossicles as they lie within with starch grains, the movements of the different parts can be readily followed under a low power microscope. When the drum is set into vibration by sound waves, it is readily seen that the whole chain of ossicles vibrates, so as to convey the vibrations to the plunger in the oval window. Many experimenters have noted the remarkable way in which the apparatus responds to vibrations varying very greatly in rate. Tones of low or of high pitch appear to be recorded with equal impartiality and fidelity. Experiment therefore confirms our sensations, which show that the ear responds to vibrations varying from 40 to 40,000 per second. It is stated that the natural period of the ossicles and drum, owing to their small size, is very much more rapid even than $\frac{1}{40,000}$ second, and it is because of this that the system is able to respond faithfully to the vibrations of longer period used in audition.

Direct observation thus shows that the ossicles form levers which together conduct the vibrations from the drum to the plunger of the oval window. It is necessary to consider the effect of this lever system on the

amplitude and force of the vibration. Motion is applied to the manubrium of the malleus and is communicated to the long process of the incus. The former is one and one-half times the length of the latter and therefore the stapes moves with two-thirds the amplitude of the drum. If the levers moved without friction, this would be accompanied by an increase in the force of the vibrations of one and one-half times. But owing to the air which surrounds the levers and thus damps their vibration, and to the energy required to set them in vibration on account of their mass, it is probable that the force of the vibrations which reaches the oval window is not more than half that incident on the manubrium. The drum, on the other hand, has an area which is about twenty times that of the oval window, and the energy incident on the drum and communicated to the manubrium is as many times greater than if the sound waves were incident on the oval window direct. But owing to the energy absorbed by the levers, the magnification is probably not greater than ten times, that is one-third of the calculated amount. Two other features of the chain of ossicles should be mentioned. In the first place it will be observed that the axis, about which the malleus and incus rotate, passes through the bones, so that the big mass formed by the articular surfaces is above, and the levers below, the axis of rotation, and the ossicles are approximately balanced. Secondly, the articulation between the malleus and incus is saddle-shaped and there is a spur on the malleus which engages with the body of the incus so that, when the tensor tympani muscle relaxes and the malleus travels outwards, the spur disengages and the incus is therefore not forced to follow. When, on the other hand, the stapedius muscle is in tonic contraction, the spur is in engagement, and vibrations are therefore communicated from one bone to the other. If, however, the force applied is excessive, owing for example to a box on the ear, then the two bones separate slightly like the limbs of a compass, and the spur passes the body of the incus without communicating the blow to it. In this way rupture of the annular seal between the plunger of the stapes and the oval window is prevented.

INTERNAL EAR

Within the petrous portion of the temporal bone are two mechanisms, anatomically in close relationship, but physiologically entirely separate. One of these mechanisms, which is called the cochlea, belongs to the auditory organ; the other, called the vestibule, consists of a series of organs which concern equilibration and have no connection with hearing.

THE LABYRINTHS lie one within the other; the outer, or osseous, labyrinth is hollowed out of the petrous portion of the temporal bone, and outlines roughly the shape of the membranous labyrinth within it. Between the two is liquid, so that, as in the case of the brain, no constraint is put by the external wall on the soft structures which it contains. This liquid is called perilymph. The membranous labyrinth consists of a series of hollow ducts and sacs, which are filled with a liquid called the endolymph. The parts of the membranous labyrinth and the relative positions which they occupy are shown in Fig. 268. From before backwards they will be seen to consist of a spiral tube, called the cochlea, the saccule, and the utricle to which are connected the three semicircular canals.

Of these structures, the cochlea alone is concerned with hearing, as the following evidence shows:

(1) Destruction of the utricle and canals causes disturbed equilibration, nystagmus and vomiting, but no deafness.

(2) Destruction of the cochlea causes deafness, but no disturbance of equilibration.

(3) Fishes, in which no evidence of hearing can be found, possess utricle, saccule and canals, but no cochlea.

THE COCHLEA is a tube 20 to 30 mm. long, which is spirally wound round a cone of bone called the modiolus, through the centre of which enters the auditory nerve. From the modiolus a spiral lamina of bone extends about two-thirds the way across the spiral bony canal, so as partially to divide it into two equal portions. From the outer edge of this lamina two membranes extend to the walls of the canal, so that the latter is divided throughout its length into three separate ducts. The upper duct is called the scala vestibuli, the middle duct between the two membranes the scala media, and the lower the scala tympani. The two membranes dividing off these ducts are quite different in structure; whereas the upper, called Reissner's membrane, is a thin layer of cells only, the lower is of complicated arrangement and is called the basilar (base) membrane. To the latter is attached, in the organ of Corti, a series of sensitive hair cells connected with the fibres of the auditory nerve, which run through the osseous spiral lamina to the body of the modiolus. To the upper edge of the spiral lamina

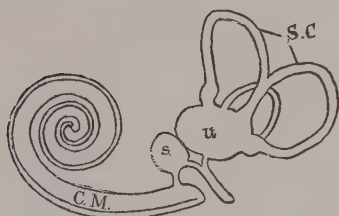


FIG. 268. The Membranous Labyrinth.

C.M. Canalis or scala media of the cochlea.

s. Sacculus.

u. Utricle.

S.C. Semicircular canals.



FIG. 269. Vertical Section through the Cochlea.

is attached a projecting ledge called the lamina tectoria; this is so mounted that it projects over, but probably does not quite touch, the tips of the hair cells. If however the basilar membrane is displaced upwards, the hairs touch the membrana tectoria, and the resulting stimuli are communicated to the auditory nerve. To prevent damage to the hairs, owing to excessive motion of the basilar membrane, rods of Corti are placed between the hair cells in such a way that, when they come in contact with the membrana tectoria, further movement of the basilar membrane is prevented.

The way in which motion is imparted to this membrane by the ossicles may be described as follows. The osseous labyrinth communicates with the middle ear by means of two openings, the oval window and the circular window. The oval window connects with the upper of the three cochlear canals, viâ the vestibule. The upper canal is therefore called the scala vestibuli. The lower canal connects with the round window only, and since the round window is fitted with a membrane, the canal gets the name scala tympani (drum or membrane). Fitting into the oval window is the plunger of the stapes, and between the two is the annular seal which permits motion of the plunger without allowing escape of the perilymph from the labyrinth. The circular window is also closed by its membrane, in order that leakage of perilymph may be prevented. When the plunger of the stapes is moved inwards under the influence of sound waves on the drum, the perilymph,

being incompressible, is driven inwards into the vestibule. From the vestibule a corresponding volume of liquid is displaced into the scala vestibuli of the cochlea. This drives Reissner's membrane downwards, and thus increases the pressure on the endolymph in the scala media. The basilar membrane therefore moves downwards and the hair cells are drawn further away from the membrana tectoria. But this movement of the basilar membrane presses on the fluid contents of the scala tympani which communicates with the round window, and therefore causes bulging of the membrane closing that aperture. Movement inwards of the plunger is therefore accompanied by movement downwards of the basilar membrane and movement outwards of the membrane of the round window and vice versa. Vibrations of the ossicles

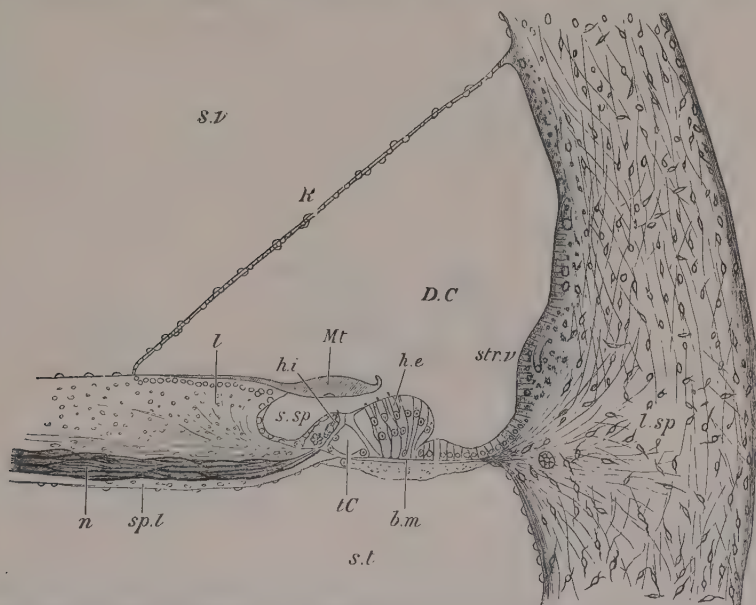


FIG. 270. Vertical Section of the first Turn of the Human Cochlea. (G. RETZIUS.)

- | | |
|---------------------------------|---|
| <i>S.V.</i> Scala vestibuli. | <i>s.sp.</i> Spiral sulcus. |
| <i>s.t.</i> Scala tympani. | <i>R.</i> Section of Reissner's membrane. |
| <i>D.C.</i> Scala media. | <i>l.</i> Limbus laminae spiralis. |
| <i>sp.l.</i> Spiral lamina. | <i>Mt.</i> Membrana tectoria. |
| <i>n.</i> Nerve fibres. | <i>t.C.</i> Tunnel of Corti. |
| <i>l.sp.</i> Spiral ligament. | <i>b.m.</i> Basilar membrane. |
| <i>str.v.</i> Stria vascularis. | <i>h.i., h.e.</i> Internal and external hair cells. |

are in this way communicated to the basilar membrane and to the hair cells, causing stimulation of the auditory nerve. The basilar membrane is composed principally of radial fibres, and varies in width from end to end of the cochlea.

The way in which these fibres vibrate under the influence of sound vibrations will be considered in the next section, but one further point remains for consideration here, namely the compensation of the cochlea against the effects of gravity and acceleration. This may be explained by considering a cochlea formed of a straight tube having the fenestra rotunda at one end and the fenestra ovalis at the other, the basilar membrane forming a diaphragm in the middle. If this tubular cochlea were so placed in the skull that the two windows were at the same level, gravity acting on the contained liquid would not cause flow to occur to either end. But if the head

were tilted so that one window was below the other, the fluid would tend to run towards the lower window. This would draw the basilar membrane over to that side, and either cause the distance between the hair cells and membrana tectoria to decrease, so that they would come into contact and thus cause stimulation of the auditory nerve with a sensation of sound, or else to increase the distance so that response to feeble sounds would be impaired. It will be seen at once that such an effect of gravity would seriously reduce the efficiency of the organ of hearing. Compensation could be to a considerable extent effected by bending the tube so that the two windows were as close together as possible. The hydrostatic pressure would thus be reduced to its smallest amount in the event of the head being tilted so as to bring one window vertically over the other. Such a bent tube would be compensated against gravity and linear accelerations in different directions, but not against angular acceleration, for on turning the head quickly from side to side a sound would be generated in the ears. In order to compensate for this effect it is necessary to bring the two limits of the tube in close apposition so that they form a U. A still higher degree of correction would be obtained if the U-tube were

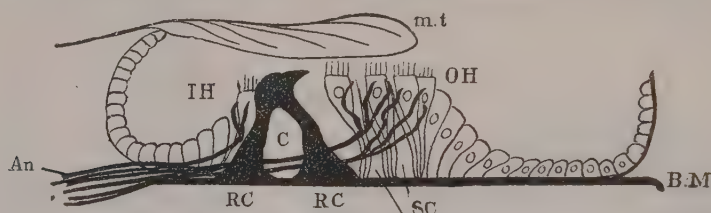


FIG. 271. Section through the End Organ of the Auditory Nerve in the Cochlea (Organ of Corti).

B.M.	Basilar membrane.	SC.	Sustentacular cells.
C.	Canal of Corti.	An.	Auditory nerve.
RC.	Rods of Corti.	m.t.	Membrana tectoria.
IH and OH. Inner and outer hair cells.			

now wound into a close spiral. But if the two limits of the U-tube were joined, with the basilar membrane forming the diaphragm between them, a very close mechanical model of the cochlea would have been obtained. The peculiar shape of the cochlea would therefore appear to be explained on the supposition that it is compensated against accelerations and gravity.

THE ORGAN OF CORTI. The end organ of the auditory nerve is represented by the organ of Corti, which rests on the basilar membrane (Fig. 271). It consists of a double row of stiff cells, the inner and outer rods of Corti, which run throughout the whole length of the scala media and are surrounded by sense epithelium, the hair cells. On the inner side of the rods of Corti there is a single row, on the outer side three rows of hair cells. The fibres of the auditory nerve pass up through the column of the cochlea, through the bipolar ganglion cells which form the spiral ganglion, and then out along grooves in the spiral lamina to end in arborisations, partly in the inner hair cells and partly among the outer hair cells. Between the hair cells are the sustentacular cells, or cells of Deiters, the peripheral processes from which join together so as to form a reticulate membrane over the hair cells, the hairs themselves projecting through orifices in the membrane. Resting on the upper surface of the membrana reticularis is the membrana tectoria. To this membrane is often ascribed a damping effect on the vibrations of the structures below. Any movement of the basilar membrane would be transmitted to the rods of Corti, and by these to the overlying hair cells.

With every vibration, these would oscillate in the line of their long axis, so that their hairs would move up and down and possibly strike against the under surface of the membrana tectoria.

Other views have, however, been advanced as to the way in which the hair cells become stimulated. Thus Wrightson states that there is a to-and-fro movement between the hair cells and the membrana tectoria, so that the hairs are bent first to one side and then to the other. Keith suggests, on the other hand, that the hairs are embedded in the membrana tectoria and that the stimuli are set up by the pulling and bending of the hairs which must occur when the basilar membrane is moved. Further research is required to elucidate this point.

NUTRITION OF COCHLEA. The organ of Corti and the surrounding structures appear to obtain nutrition from three different sources. (1) Arterial twigs pass with the cochlear branch of the auditory nerve, and traverse the foramina in the spiral lamina alongside the outgoing nerve fibres, to join with several arteries which run round the inside of the cochlea. The largest of these vessels is found in the scala media. Minute branches pass from these to the hair cells, etc., the venous blood being collected in corresponding veins. (2) The outer wall of the scala media is highly vascular, a network of capillaries lying under the epithelium. It is probable that oxygen and food pass by diffusion into the endolymph through the epithelium, and that waste products are removed in the same way. (3) Perilymph secreted in the utricle and saccule passes up the scala vestibuli to the top of the cochlea, then through a minute pore called the helicotrema into the scala tympani below, and back along this canal to escape from the internal into the middle ear by a minute opening below the round window. The helicotrema is apparently large enough to insure that the mean pressure in the scala vestibuli shall be equal to that in the scala tympani, but not so large that the momentary differences in pressure, caused by the movements of the stapes, are obliterated.

3.—AUDITORY SENSATIONS

THEORIES OF HEARING

HELMHOLTZ' THEORY was that the organ of Corti and the basilar membrane together form a series of automatically recording resonators. In the same way that each of the strings of a piano can be set into vibration by the sounding of a note which corresponds with it in pitch, so also can the different fibres of the basilar membrane vibrate to a certain note, and so cause stimulation of the hair cells which are attached to it.

Four objections have been made to this theory. (1) That the fibres of the basilar membrane are so short that they could not respond to the low notes which the ear is able to hear. The answer to this criticism is that not only the length, but also the tension and weight of a cord determine its vibration rate. In the case of the basilar membrane the tensions in the fibres are probably minute, while the weights of the arches of Corti and the hair cells must make the period of vibration so much the longer.

(2) That the separate fibres of the basilar membrane are bound together so that vibration of the separate fibres would be impossible. This objection was met by the calculation, by Helmholtz, that a uniform membrane, in which the tension was greater from side to side than longitudinally, would be able to respond in the manner required.

(3) That the difference in length of the fibres is not sufficiently great for the short ones to vibrate to notes of 4,000 vibrations per second, while the long ones vibrate to 40 vibrations per second only. This objection also fails when we reflect that not only length, but also tension and weight determine the period of vibration of a stretched cord. However accurately we can determine length and weight by histological examination, the method tells us nothing concerning tension. This objection therefore does not prevail.

(4) That if the cochlea depends for its action on the resonance of the

basilar fibres, we should expect a musical note to seem to go on sounding after the note has actually ceased. Since, on the other hand, we know from our own experience that words such as 'utter,' in which there is an interval of silence between the two 'ts,' are quite different from 'udder,' in which there is no interval of silence, it follows that the fibres of the basilar membrane have not been in vibration after the sound ceased, and therefore probably resonance of the basilar membrane is imaginary. But if we suppose the fibres to be highly damped, so that they come to rest at once when the note ceases, how comes it that they can be set in motion so readily that in only three or four vibrations a note is distinctly heard? The answer is probably obtained from the fact that the cochlea is filled with liquid. This liquid makes the basilar membrane 'dead beat,' because movements, when the liquid is still, set up eddies which quickly check the motion owing to the viscosity of the liquid. On the other hand, when a sound is entering the ear, and the fluid is therefore in motion, this movement is the more rapidly imparted to the basilar membrane because of its continuity, but even if it consisted of separate fibres it would still be set promptly into vibration owing to the viscosity of the liquid. In this way one can explain both the rapid response and the rapid damping of the cochlea.

In favour of Helmholtz' theory we have the following evidence :

(1) In boiler-makers' disease we have inability to hear high notes, and we find that it is the short fibres of the basilar membrane which have degenerated.

(2) In experiments in which the ears of animals have been stimulated for long periods by the same note, subsequent examination has shown the localisation of degeneration to one part of the organ of Corti. With a high note the short fibres are affected, with a low note the long.

(3) If one of the ears be fatigued by prolonged stimulation to a constant note, its response to the same note is found to be inhibited, but notes of slightly longer or shorter pitch are found to be unaffected. This shows clearly that the response to a given rate of vibration must only affect a certain limited number of hair cells and nerve fibres, and is therefore strongly in favour of Helmholtz' theory.

(4) Animals whose calls have a small range of pitch (*e.g.* birds) have short basilar membranes which vary but little in length.

(5) Animals in which different parts of the cochlea have been destroyed, appear to give definite evidence for deafness to high notes when the short basilar fibres are damaged, and deafness to low notes when the long fibres have been removed.

(6) Patients are found in whom there are islands of deafness, that is, they are deaf to a limited part of the musical scale. The Helmholtz theory readily explains these cases as being due to local disease of certain basilar fibres or their corresponding hair cells. Further, there are cases in which the two ears give different notes, a condition called double disharmonic hearing. This is easily explained by a change in the natural period of the fibres of the basilar membrane in the diseased ear, as the result either of stretching or of increased mass due to inflammation.

(7) McKendrick was able to produce a model of the cochlea with basilar membrane and organ of Corti. He found, as the Helmholtz hypothesis requires, that parts of the membrane can be made to vibrate to a certain pitch and not to others. Wilkinson has recently come to the same conclusion.

(8) McKendrick calculated that the number of fibres in the auditory nerve, the number of fibres in the basilar membrane and the number of hair cells and arches of Corti were sufficient to give the total number of different pitches (about 11,000) in the auditory scale.

It would appear, therefore, that the evidence in favour of Helmholtz' theory is very convincing. Other hypotheses have been proposed, however, which will now receive brief consideration.

RUTHERFORD'S HYPOTHESIS compares the cochlea with a telephone. In the same way as the diaphragm of the receiver is set into vibration by the sound waves, and starts corresponding variations in the strength of the current conducted to the transmitter, so the vibration of the basilar membrane as a whole causes impulses to be sent up the auditory nerve which correspond with the air vibrations received by the ear. Analysis does not take place in the cochlea at all, but in the brain. Wrightson, who has restated this theory and added much detail to it, states that the cerebral analysis is effected by differences between the time intervals of the points of zero pressure and of the maximum plus and minus pressures.

The following objections may be stated against the Rutherford-Wrightson hypothesis :

(1) It assumes that the auditory nerve can conduct complicated wave forms, intact as to pitch and amplitude, at rates up to 40,000 vibrations per second. Rutherford, in this connection, pointed to the motor nerves of the bee's wing, which are capable of responding to transmitted impulses at 460 per second. Between 40,000 and 460 is, however, a big gap which will certainly have to be bridged before this view as to the transmission of the vibrations intact to the brain can be accepted.

(2) We cannot picture a cerebral apparatus which can analyse these complicated nerve impulses even if they could reach it, and neither Rutherford nor Wrightson assist us to do so. The relegation of the powers of analysis to the cerebral cortex is, at the present at any rate, equivalent to giving up any attempt to explain the power of analysis possessed by the organ of hearing.

(3) It would seem that a very much simpler organ than that of the cochlea would be sufficient to convert sound waves into nerve impulses, if no analysis of the stimulus took place there.

(4) It would be very difficult to explain, on this hypothesis, the localisation of deafness to certain notes, which accompanies disease of part of the organ of Corti.

(5) This hypothesis does not explain why fatigue to one note leaves the response to all other notes apparently unaffected in intensity.

The objections to this hypothesis are therefore of a formidable character. Much additional evidence in its favour would be necessary to place it even on a par with the theory of Helmholtz.

WALLER'S HYPOTHESIS, recently elaborated by Ewald, stated that the basilar membrane vibrated in the form of pressure patterns, which are similar to those which may be seen on a vibrating plate. Ewald found by experiment that the patterns take the form of equidistant stationary nodes or ridges, the distance between which varies with the pitch of the note entering the mechanism. The distance between the nodes is measured by the hair cells, and corresponding impulses are sent to the auditory centre. The advantage of this hypothesis is, that like that of Helmholtz, it places the analysis of the sound waves in the cochlea and therefore does not, like Rutherford's hypothesis, require the transmission by the auditory nerve of rapid impulses or the analysis of such impulses by the brain. It is clear, however, that so far as our present knowledge goes the evidence is all in favour of the Helmholtz view.

BEATS AND DISSONANCE. The overtones of any sound, at any rate the lower ones, are at considerable distance from one another on the musical scale, and therefore differ considerably in the number of vibrations of which they are composed. If we sound two tuning forks, the vibrations of which differ only by one or two per second, the phenomenon known as 'beats' is produced. This is due to the summation and interference of the waves from the two tuning forks. Let us suppose we have tuning forks vibrating, one at 100 and the other at 101 times a second, and that they begin vibrating together. At first the waves of compression started by each fork will coincide, so that the total compression of the air at each beat will be the compound effect of the compression produced by the two forks, which will reinforce one another. After the lapse of half a second the tuning forks will be at different phases of their excursion. The 101 fork will be moving in one direction while the 100 fork is moving in the other, so that the compression produced by one fork coincides with the expansion of the air produced by the moving backwards of the other fork. The sound produced by one fork is therefore diminished by the sound produced by the other fork, and the

total sound is less than either of the two forks. At the end of one second, the phases of the two forks once more corresponding, we shall get the sound increased in loudness; thus there is an alternate waxing and waning of the sound which recurs once a second and is spoken of as a 'beat.'

The number of beats per second may be used to determine the differences in the vibration frequencies of two forks. Thus, two forks vibrating, one at 100 and the other at 110, will give ten beats per second. As the number of beats increases, the effect produced on the ear becomes more and more disagreeable, just as the rapid alternation of illumination produced by a flickering light is disagreeable to the eye. This objectionable character of the sound is most marked when the beats recur at about thirty-three times per second; the individual beats are not then distinguished, but we speak of the sound as discordant or *dissonant*.

CONSONANCE. The opposite condition of *consonance* or harmony involves therefore, in the first place, an absence of beats, *i.e.* of rhythmic oscillations of amplitude of sound waves which reach the ear. The constituent tones and overtones must be capable of being combined into a compound wave of regular amplitude and rhythm. In the most complete consonance, the component notes are identical, at any rate as concerns the greater number of their overtones. The most complete consonance is attained when the two notes which are sounded together are identical. Almost as complete is the consonance obtained when a note is sounded together with its octave. The other consonant intervals which are employed in music are as follows:

1:2	.	.	.	.	.	.	.	.	Octave
2:3	.	.	.	.	.	.	.	.	Fifth
3:4	.	.	.	.	.	.	.	.	Fourth
4:5	.	.	.	.	.	.	.	.	Major third
5:6	.	.	.	.	.	.	.	.	Minor third
5:8	.	.	.	.	.	.	.	.	Minor sixth
3:5	.	.	.	.	.	.	.	.	Major sixth

It will be noticed that in all these consonant combinations, the vibration frequencies of the notes are in proportion to small whole numbers. If we put down not only the fundamental tones of these notes, but also their overtones, we shall see that there is considerable identity as regards the latter. In the case of the octave the two are almost identical, the only difference being the ground tone of the lower note, and the identity diminishes as we pass from the octave through the thirds to the sixths. The overtones which are identical are shown by black type:

Overtone											
$\frac{1}{2}$	{	1	2	3	4	5	6	7	8	9	10
		D	2	S	4		6		8		10
$\frac{2}{3}$	{	2	4	6	8	10	12	14	16	18	20
		D	3	S	6	9	12	15	18		
$\frac{3}{4}$	{	3	6	9	12	15	18	21	24	27	30
		D	4	S8	12	16	20		24	28	
$\frac{4}{5}$	{	4	8	12	16	20	24	28	32	36	40
		D	5	S10	15	20	25	30	35		40
$\frac{5}{6}$	{	5	10	15	20	25	30	35	40	45	50
		D	6	S12	18	24	30	36	42	48	
$\frac{3}{5}$	{	3	6	9	12	15	18	21	24	27	30
		D	5	S	10	15	20		25		30
$\frac{8}{9}$	{	8	16	24	32	40	48	56	64	72	80
		D	9	S18	27	36	45	54	63	72	
$\frac{8}{15}$	{	8	16	24	32	40	48	56	64	72	80
I 5	{	D	15	S	30	45	60		75		90

D = difference tone. S = summation tone.

D = difference tone.

S = summation tone.

It will be observed that in all cases, with the exception of the octave, the summation tone is discordant with the other partial tones.

In the second and seventh, which are discordant, it is only the eighth overtones which are identical, while the fundamental tones will as a rule be so close together that beats of a number calculated to give dissonance will be produced. Since the phenomenon of beats depends on the absolute number of vibrations per second, they are more easily produced by two notes near together at the lower end of the scale than at the upper end. Thus the dissonance is quite perceptible in a major third at the lower end of the piano, but disappears at the upper part, since here the beats produced are so rapid that they become imperceptible.

The various notes used in music are obtained by employing the consonant intervals which we have given above. The major chord is composed of the fundamental tone, the major third and the fifth. If we take 'c' as the fundamental tone, the notes of the chord are c, e, g, with vibration frequencies corresponding to $1, \frac{5}{4}, \frac{3}{2}$, i.e. 4, 5, 6. The major chord from g is g, b, d, i.e. three notes with vibration frequencies corresponding to $\frac{3}{2}, \frac{15}{8}, \frac{9}{4}$, i.e. 4, 5, 6. The major chord from the fourth, f, is f, a, c, with the vibration frequencies $\frac{4}{3}, \frac{20}{12}, \frac{12}{6}$, i.e. 4, 5, 6. The C major scale is therefore as follows :

C	D	E	F	G	A	B	C	
1	$\frac{9}{8}$	$\frac{5}{4}$	$\frac{4}{3}$	$\frac{3}{2}$	$\frac{5}{3}$	$\frac{15}{8}$	2	} Major scale
1	$\frac{9}{8}$	$\frac{6}{5}$	$\frac{4}{3}$	$\frac{3}{2}$	$\frac{8}{5}$	$\frac{15}{8}$	2	

Different instruments are tuned to one normal note, i.e. to A with 440 vibrations per second (this note varies somewhat in different countries). Taking this as the normal, the vibration frequencies of the various notes used in music are given in the following Table :

Notes.		Vibrations per second.						
C	.	33	66	132	264	528	1056	2112
D	.	37.125	74.25	148.5	297	594	1188	2376
E.	.	41.25	82.5	165	330	660	1320	2640
F.	.	44	88	176	352	704	1408	2816
G.	.	49.5	99	198	396	792	1584	3168
A.	.	55	110	220	440	880	1760	3520
B.	.	61.875	123.75	247.5	495	990	1980	3960

COMBINATION TONES. If two tuning forks, with an interval of one-fifth between them, are sounded together, we may hear a weak lower tone, the pitch of which is an octave below that of the lower fork. This is known as a 'combination tone.' The combination tones are divided into two classes : (1) 'difference tones,' in which the frequency is the difference of the frequencies of the generating tones ; (2) 'summation tones,' which have a pitch corresponding to the sum of the vibrations of the tone of which they are composed. By means of appropriate resonators these tones can be reinforced, showing that they have an objective existence and are not produced in the ear itself.

Not only can the ear appreciate differences between different musical instruments, dependent on the varying overtones present in the sound produced by each instrument but, when a number of these instruments are

sounded simultaneously, the ear can pick out from the compound sound the notes due to the individual instrument ; and a person with a trained ear can with ease name notes composing any chord struck on an instrument such as the piano.

OHM'S LAW. This power of analysis, which is possessed by the ear, or at any rate by the auditory apparatus, may be stated in the form of the law, known as Ohm's law, which is as follows :

"Every motion of the air which corresponds to a composite mass of musical tones is capable of being analysed into a sum of simple pendular vibrations, and to each single vibration corresponds a simple tone, sensible to the ear and having a pitch determined by the periodic time of the corresponding motion of the air."

SOUND LOCALISATION. Experiment shows that man and animals can appreciate with fair accuracy the direction from which a sound is coming. There has been considerable speculation as to how this information is obtained and, although the subject has not been completely elucidated, it appears to have been established that the following factors are important :

(1) The intensity of the sounds entering the two ears. When a sound is coming from one side, the ear on that side receives the more powerful stimulus.

(2) The relative intensities of the components of high and low pitch vary with direction, because the notes of long wavelength (low pitch) will be diffracted the more readily round the head to the ear away from the sound than will those of short wavelength (high pitch).

(3) The sounds reaching the nearer ear will arrive earlier than those stimulating the other, because of the time taken to travel round the head. The nerve impulses from the two ears will therefore not arrive at the same instant, and by an appreciation of the difference in time, the approximate position of an external object can be gauged.

That this factor is of great importance can be shown by experiment in the following manner : A stethoscope with two earpieces is fitted in position, and to its mouthpiece is applied a loud tuning fork. The tube connecting the mouthpiece to one of the earpieces has an adjustable U-piece like a trombone, so that the distance travelled by the sound in reaching that ear can be varied. The other tube has a length which is equal to that of the others, with the U-piece in its mid position. When a note is sounded and the U-piece altered, the position of the sound appears to move from one side to the other according to which ear has the shorter tube.

(4) The sounds reaching the ears travel not only through the air, but also through the bones of the skull. This can be proved by placing a tuning fork, which has been sounded and allowed to fade until its note is inaudible, on one of the teeth ; the sound will be conveyed by the root of the tooth to bone, and by bone conduction to the ears. Therefore, when a sound enters the right ear, it will travel by bone conduction to the left and, owing to its rate of travel being different from that in air, will reach the left ear at a different instant from that at which the sound travelling round the head will reach it. If one ear is facing the sound, the bone-conducted sound will probably reach the other ear before the air-conducted does. On the other hand, when both ears are equidistant, it is clear that the air-borne sound will arrive first at both ears, and the bone-conducted sound very much later. By an appreciation of the difference in time of the arrival of the two sounds it is probable that localisation is aided.

(5) In animals, the ability to turn the ears in different directions and so find the direction of maximum intensity must be of the utmost possible value in sound localisation.

CHAPTER XXV

CUTANEOUS SENSATIONS

THE skin, being the outermost layer of the body, represents the tissue or organ by which the organism is brought into relationship with its environment. In the widest sense of the term the skin is protective. This function it discharges by virtue not only of its physical properties, but also of its rich endowment with sense organs, by means of which the intracorporeal events can be correlated with those occurring outside and immediately affecting the organism.

We are accustomed to distinguish several qualities of sensation among those having their origin in the skin, the chief of which are the sense of touch, including that of discrimination, the sense of pain and the sense of temperature. The very different qualities of sensation included under these three classes suggest that there may be a special mechanism, or class of mechanism, for each sense, and a careful investigation of the sensory qualities of the skin surface bears out this idea. Isolated stimulation of minute areas on the skin does not excite all the sensations together, but only a sense of touch or of pain, or a sense of cold or warmth. We are therefore justified in dealing with each of these sensations separately.

THE TEMPERATURE SENSE

By means of the skin we can appreciate that a body coming in contact with it is either cold or warm. If the body is at the same temperature as the skin, as a rule no sensation of temperature is excited. It was formerly thought that the sensations both of heat and cold were determined by the excitation of one and the same end organ. Warming of this end organ would produce a sensation of warmth, while a diminution of its temperature would produce the sensation of cold. Careful investigations by Blix and Donaldson of the distribution of the temperature sense has shown that this opinion cannot be maintained. If a small surface warmed to a few degrees above the temperature of the skin be moved over any part of the surface of the body, *e.g.* the back of the hand, it is found that the warmth of the instrument is not equally appreciable at all parts of the surface of the skin. At some points the sensation of warmth will be very pronounced, but between these points the sensation of warmth may be entirely wanting and the instrument may be judged to be of the same temperature as the hand itself. In this way a series of 'warm points' may be mapped out. On now cooling the instrument a few degrees below the temperature of the surface of the body and then moving it over the surface in the same way, it will be found again that the coolness of the instrument is appreciated only at certain points which can be regarded as 'cold points' and as containing the nerve endings by the excitation of which the sensation of cold is produced. If the warm points be pricked out in red ink and the cold points in blue ink, it will be seen that they do not in any way correspond.

A convenient instrument for this purpose is the one invented by Miescher, consisting of two tubes cemented together and communicating at a small flattened extremity,

which is applied to the surface of the skin ; through the tubes water can be led at any desired temperature, which is read off by a thermometer placed within the tube. Having mapped out the warm spots, it may be shown that they are excitable by means of mechanical or electrical stimuli and that the sensation produced is the same as if they had been excited by their adequate stimulus, viz. a rise of temperature.

EXACT LOCATION of the spots is rendered difficult by the irradiation of the sensation produced, so that it is difficult to refer the sensation of warmth or cold definitely to the point stimulated. An investigation of the topography of these warm and cold spots shows that the apparatus for the appreciation of cold is much more extensively distributed over the body than that for the appreciation of warmth, as is evidenced from the diagram (Fig. 272) giving the topographic distribution of the cold and warm sense organs on the palm of the hand. Waterston (1923) claims that in the case of both heat and cold, the topographic distribution of the spots alters continually. In skin suffering from a mild erythema, all parts respond to warmth, that is, all signs of a punctate arrangement have gone. He concludes that all parts of the skin can respond to both heat and cold, the punctate

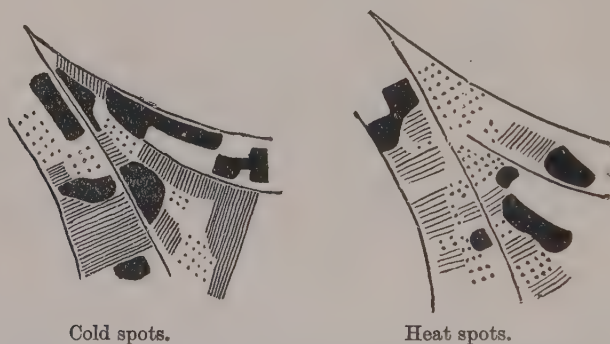


Fig. 272. Heat and Cold Spots on part of Palm of right Hand.

The sensitive spots are shaded, the black being more sensitive than the lined, and these than the dotted parts. The unshaded areas correspond to those parts where no special sensation was evoked. (GOLDSCHIEDER.)

arrangements found at a single examination being due to some parts being more active than others. The skin capillaries are stated to show a similar change from time to time in the quantity of blood which they transmit. The temperature sense is best marked in the following regions of the body : the nipples, chest, nose, the anterior surface of the upper arm and the anterior surface of the fore-arm, and the surface of the abdomen. It is much less marked on the exposed parts of the body, such as the face and hands, and is but slight in the mucous membranes. Thus it is possible to drink hot fluid, such as tea, at a temperature which would be painful to the hand, and still more to any other part of the body. The scalp is also very insensitive to changes of temperature. The acuteness of the temperature sense varies considerably with the condition of the skin and with the previous stimulation of the sense organs. The sense is most acute at about ordinary skin temperature, i.e. between 27° and 32° C. At this temperature the skin can appreciate a difference of $\frac{1}{5}^{\circ}$ C. When the skin is very cold or very hot, the temperature sense is not nearly so delicate. This sense presents the phenomenon of adaptation in a marked degree. It is a familiar experience that, on coming from the external air on a cold day into a warm room, a sensation of warmth is experienced all over the body.

In a few minutes this sensation wears off. On now leaving the room to go outside again, the sensation of cold is at once appreciated, to disappear in its turn after a few minutes. The effect of adaptation is still better shown by the experiment of taking three basins of water, *a*, *b*, and *c*; *a* contains cold water, *b* tepid water, *c* hot water. The left hand is immersed in the cold water and the right hand in the hot water for a few minutes. On now placing both hands into the basin of tepid water, it feels hot to the left hand and cold to the right hand. Such experiences as this led Weber to the conclusion that the essential stimulus for the temperature sense was not the actual temperature to which the sense organs were subjected, but the fact of a change of temperature. He imagined that, while the temperature sense organs were being warmed, a sensation of warmth was produced, and when their temperature was being lowered, a sensation of cold. Such a theory, however, would not account for the fact that, above a certain temperature, water may feel warm and the feeling may continue so long as the skin continues to be stimulated. On a cold day the air may feel cold to the face and the feeling may last the whole time that the face is exposed. Moreover we have in the temperature sense, conditions which remind one of the after images which occur in the eye. If a penny be pressed on the forehead and then removed, the sensation of cold lasts some little time after the penny has been removed. In this case a sensation of cold is produced although the end organs are being gradually warmed up after the removal of the penny. In order to account for these facts Hering, at a time when the differentiation of hot and cold spots had not yet been effected, suggested that the temperature sense organs could be regarded as having a zero point at which no sensation was produced. If their temperature was raised above this point, a sensation of warmth was produced, and vice versa. The zero point, however, was not a fixed one, but could move upwards to a certain extent on prolonged exposure to high temperature, or downwards on prolonged exposure to a low temperature. In the light of the researches of Blix and Goldscheider, we should have to apply Hering's theory of a zero point to each of the temperature end organs separately.

A cold pencil passed over a warm spot evokes no sensation whatsoever. If, however, a pencil considerably warmer than the skin be passed over a cold spot, this may be excited so that the paradoxical result is produced of a sensation of cold as the result of stimulation by a warm body. It is a familiar fact that the immediate effect of entering a hot bath is very much the same as that of entering a cold bath, viz. a rise of blood pressure and contraction of the unstriated muscles of the skin and hair follicles with the production of 'goose skin.' It has been suggested that the distinctive quality of a sensation of *hot* as compared with that of *warm* is due to the simultaneous stimulation of warm spots and cold spots. When testing the distribution of the temperature sense, it is found that the sense of cold is evoked more promptly than that of warmth. This is interpreted as showing that the end organs for the warm sense are situated more deeply than those for cold. We have no evidence as to the histological identity of these organs.

THE SENSE OF TOUCH

By means of the sense of touch we arrive at a conclusion as to the qualities, such as shape, texture, hardness, &c., of the bodies with which the skin is in contact. In this judgment, however, very many other sensations

are involved besides those which can be regarded as strictly tactile. Thus, the hardness of an object signifies its resistance to deformation, besides its power of deforming the skin surface with which it is in contact; the former quality, *i.e.* of resistance, is one which involves the muscular sense, since we judge of it by the extent to which we can move our muscles without causing any alteration of the surface of the object.

The tactile sensibility of the skin as a whole, like its temperature sensibility, was thought to have a punctate distribution. Recent work on the subject, by Waterston (1923), throws very great doubt on the validity of this idea.

RESPONSE TO DIFFERENT STIMULI. The adequate stimulus for the tactile nerve endings is not so much pressure, as deformation of surface. It appears to matter little whether the surface be deformed by pulling it or by pushing an instrument into it. The ineffectiveness of mere pressure is shown by dipping the finger into a vessel of mercury. The sensation of pressure is noted only at the point where the finger passes through the surface of the mercury, and this is the only part where there is an actual deformation of the skin, due to the sudden passage from the pressure of the mercury to the negligible pressure of the outside air. The tactile apparatus is smarter in its response than any other of the sense organs. On this account stimuli

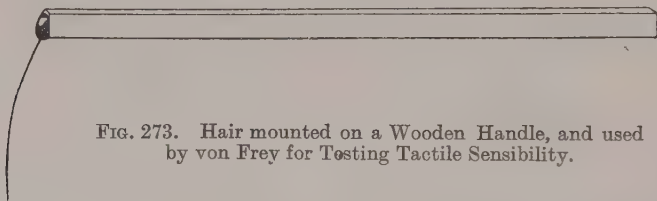


FIG. 273. Hair mounted on a Wooden Handle, and used by von Frey for Testing Tactile Sensibility.

are still perceived as discrete, when they are repeated at a rhythm which would result in complete fusion in the case of any of the other sense organs. Thus if a bristle be attached to a tuning fork and allowed to press on the skin, the vibrations of the fork are perceived by the ear as a continuous sound and by the skin as a series of discontinuous taps. Faradic currents when applied to the skin can be perceived as separate when repeated at the rate of 130 per second. The sensations evoked by placing the finger against the edge of a cog-wheel do not become continuous until the wheel is revolving at such a rate that the stimulation on the skin by the serrations occurs at a greater rate than 500 or 600 per second. The tactile apparatus resembles all the other skin sense organs in showing adaptation. A stimulus after continuing for some time may become ineffective. We are usually entirely unaware of the stimulation of our skin by the pressure of the clothes, and even an unwonted stimulation, such as that of the mucous membrane of the mouth by a plate carrying artificial teeth, though almost unbearable during the first day, rapidly becomes less, and in a few days it is not perceived at all.

In order to test the sensitiveness of touch we may use the method introduced by Hensen, *viz.* the bending of a glass-wool fibre. We can determine the pressure at which any given fibre will bend, and if we find by trial the fibre which just evokes sensation when pressed on the skin, we know exactly the force which we are applying to the skin. Von Frey employed hairs of different thickness for the same purpose (Fig. 273). The

following represents the minimal excitability of the surface of different parts of the body when tested in this way :

	Grm. per sq. mm.
Tongue and nose	2
Lips	2.5
Finger-tip and forehead	3
Back of finger	5
Palm, arm, thigh	7
Fore-arm	8
Back of hand	12
Calf, shoulder	16
Abdomen	26
Outside of thigh	26
Shin and sole	28
Back of fore-arm	33
Loins	48

The sensitiveness of the sense organs in the skin is probably much greater than that of the nerve trunks themselves. Thus Tigerstedt found that the minimal mechanical stimulus necessary to excite the exposed nerve amounted to 0.2 grm. moving at 140 mm. per second. For the touch spots, von Frey found that 0.2 grm. moving at 0.17 mm. a second is an adequate stimulus.

In testing the sensibility of any surface, it is important to remember that the hairs themselves form very effective tactile organs. The touch spots are distributed in greatest profusion around hair follicles, and there is a rich plexus of nerve fibres round the root of each hair. A slight touch applied to the hair acts on these as on the long end of a lever, the hair being pivoted at the surface of the skin, so that pressure on the hair, increased five or more times in force, is transmitted to the hair follicle and the surrounding nerve endings. The actual sensibility of any part is therefore much diminished by removal of the hairs. On 9 sq. mm. of the skin, from which the hairs had been shaved, the minimal stimulus necessary to evoke a tactile sensation was found to be 36 mg., whereas on the same surface before it was shaved 2 mg. was effective.

WEBER'S LAW. The smallest increment or decrement of stimulus which determines a perceptible difference of sensation must, according to Weber's law, always bear the same ratio to the whole stimulus. In measuring such differences it is best to apply the stimulus successively to the same surface of the skin, rather than simultaneously to adjoining areas. The time interval between two successive stimuli should not be more than five seconds and the duration of the stimuli should be equal. Weber found that in the terminal phalanx of the finger the minimal perceptible difference was about one-thirtieth, but the ratio was not the same for all regions of the skin nor for all individuals. The following represents the liminal difference in various skin regions :

Forehead, lips and cheeks	1/30th to 1/40th
Back of fore-arm, of leg and of thigh ; back of hand, and first and second phalanx of finger, &c.	1/10th to 1/20th
All parts of the foot, leg and thigh	more than 1/10th

THE SPATIAL QUALITY OF TOUCH. DISCRIMINATION. If any part of the skin be stimulated, the subject of the experiment can tell at once the exact situation of the excited spot. If two points be stimulated simultaneously, excitation is perceived as double, *i.e.* as proceeding from two points, provided the distance between the points exceeds a certain amount,

varying in different parts of the body. The power of discrimination, *i.e.* of judging whether a stimulus is single or double, can be tested by arming the points of a pair of compasses with small pieces of cork and then seeing how far apart the points must be when pressed on the skin in order that the stimulus may be perceived as double. The following Table represents this distance for various regions of the body :

DISTANCE IN MM.	
Skin region.	mm.
Tip of tongue	1.1
Volar surface of finger tip	2.3
Dorsum of third phalanx	6.8
Palm of hand	11.3
Back of hand	31.6
Back of neck	54.0
Middle of back, upper arm, and thigh	67.1

When touch spots are sought out for stimulation with the points of a compass, the distance at which the excitation is perceived as double is much diminished, as is shown by the following Table of distances for the touch spots in millimetres :

Skin region.	Distance of touch spots.
Volar side of finger tips	0.1
Palm of hand	0.1
Fore-arm (flexor side)	0.5
Upper arm	0.6
Back	0.4

The compass points are perceived to lie apart with a special distinctness when they are applied to touch spots lying on different lines which radiate from the hair follicles. The figures given in the first Table have no relation to touch spots, but show the average distance over which an excitation can be perceived as double.

The delicacy of discrimination of any part is largely associated with its mobility. Thus in the arm the delicacy increases continuously from the shoulder to the finger tip. If the localising power for touch on the shoulder be taken as 100, that of the finger tips will be represented by 2582. In the same way there is a continuous decrease of the distances of discrimination as we pass along the cheek from the ear to the lip, *i.e.* from the non-mobile to the mobile part. The power of discrimination is increased to a certain extent by practice and largely diminished by fatigue. Any factor which diminishes the tactile sensibility of the part, such as cold, will also diminish the power of discrimination.

LOCALISATION OF TOUCH. The fact that we can localise the point of stimulation shows that every tactile sensation derived from the surface of the body, besides the qualities of intensity and extensity, has also associated with it a characteristic quality dependent on its position. This localised quality of a tactile sensation was called by Lotze 'local sign.' Among psychologists there has been much discussion as to how far this local sign is an inborn attribute of the sensation of every point on the body surface, or how far it is acquired by experience and based on memory of movements and muscular impressions. In the retina we have a sense organ which, like the skin, possesses local sign but in far higher degree, the power of discrimination of the retina being three thousand times as great as that of the most sensitive part of the skin. Cases of congenital cataract occur in which the

subjects have been blind from birth. By extraction of the cataract we can give such persons the power of sight. It is found that at first there is no power of localising visual impressions. The local sign is developed only in response to experience, by comparing simultaneous visual, tactile and motor sensations. By analogy we might ascribe the local sign of cutaneous sensations to a similar causation. Our study of the spinal animal has indeed given us a physical or histological conception of local sign. We know that stimulation of any part of the body evokes an appropriate reaction, the nature of which is determined by the central connections of the entering nerve fibres. A fibre entering at one segment must therefore come into relation with a different set of motor cells from those which are set into action by a fibre entering one segment lower down. Every nerve fibre from the skin will therefore have an appropriate complex of motor paths in functional connection with its central endings; and when the activity of these reflex paths comes to be represented in consciousness, it is evident that the sensation derived from any one point must differ from that derived from any other point of the skin, by virtue of the differing motor events actually or potentially excited from the two points. In ascribing local sign to coincident muscular sensations and to the memory and experience of past movements, we are therefore giving but an imperfect explanation; since the difference between the sensations from different parts, which is at the bottom of our powers of localisation, has its origin in the structure of the central nervous system itself and is present from the very beginning of the evolution of a reactive nervous system.

PROJECTION OF TOUCH. Since the alterations in the surface of the skin which give rise to tactile sensations are habitually caused by contact with external objects, we come to regard the sensations themselves, not as changes in the skin, but as qualities of the object which touch the skin, *i.e.* we project the sensation. The projection is, however, not so great as in the case of visual sensations. Cutaneous sensations we always consider as qualities of an object immediately affecting and altering the condition of ourselves, whereas the visual sensations are referred at once to objects lying right away from ourselves, so that we are not aware that any change has taken place in our bodies as a result of the entering of rays of light into the eye.

It is remarkable to what extent projection of touch sensation may occur. Thus a surgeon actually lengthens his fingers by using a probe. When he is probing for dead bone he feels the grating of the bone, not at his finger tips, but he projects the sensation to the end of the probe. In the same way tactile sensations evoked by the contact of bodies with the insentient endings of hairs are referred to the ends of the hairs rather than to the hair follicles where the nerve impulses actually come into being.

The dependence of local sign on habitual experience is shown by the various tactile illusions, such as the well-known experiment of Aristotle. If with the eyes shut we cross the first and middle fingers and bring them in this position in contact with a pea, we should at once say that two peas lay under the fingers. This is especially marked if the pea be rolled between the fingers. The two sides of the fingers which come in contact with the pea usually touch two different objects, and these parts of the skin would have to be re-educated, *i.e.* their local sign would have to be changed in accordance with the changed conditions, before the pea would be perceived in its true state as single.

THE PAIN SENSE

When the pressure of a hard object on the skin is increased beyond that necessary to evoke a tactile sensation, at a certain pressure the quality of sensation changes and it becomes painful. For the evolution of the race as well as for the preservation of the individual this pain sense is all-important; it is the expression in consciousness of the reflexes of self-preservation which can be evoked in the spinal animal by stimuli which are nocuous, *i.e.* calculated to do actual damage to the tissues of the body. Thus when a sharp point is pressed on the skin, the sensation becomes painful just before the pressure is sufficient to cause penetration. The so-called trophic lesions, which occur in parts devoid of sensation, are determined for the most part by the lack of the pain sense and the consequent failure of the preservative reflexes of the part. It is remarkable that pain may result from changes in organs which are devoid of ordinary sensibility. Thus the intestine may be cut, sewn or handled without arousing any sensation whatsoever. A strong contraction of the muscular wall or increased distension of the gut will, however, evoke a griping pain. In the same way the ureters, which are normally devoid of sensation, can give rise to excruciating agony when they are contracted firmly on a retained calculus.

We are accustomed to distinguish many different qualities of pain, but on analysis it will be found that these qualities depend on the nature of the sense organ which is simultaneously stimulated. Thus a burning pain denotes simultaneous stimulation of the pain sense and of the nerve endings to the warm spots. A throbbing pain results when the vessels of the part are dilated and the part is tense with effused lymph, so that each pulse of the vessels causes an exacerbation of the painful stimulation and perhaps also stimulation of the tactile end organs.

The sense of pain has often been ascribed to over-maximal stimulation of any form of sensory nerve. Although it is true that over-stimulation of the auditory or optic nerve by a loud sound or a bright light may be extremely unpleasant, the sensations evoked do not partake of the characters of painful sensations such as would be produced by pricking or burning the skin. Moreover a careful investigation of the sensory points on the skin brings out the fact that there are, besides the tactile and temperature spots, other spots from which only painful sensations can be evoked. We have seen already that over-stimulation of a touch spot does not, as a matter of fact, cause pain. The pain spots which are distributed among the touch and temperature spots are insensitive to a low grade of stimulus. As the strength of the stimulus is increased, a point is suddenly reached at which the sensation evoked is painful. Moreover, in parts of the body, tactile and temperature sense are entirely wanting, though painful impressions can be easily evoked. The best example of this is seen in the cornea, minimal stimulation of which evokes pain, but nothing which can be regarded as a tactile sensation. The specific quality of pain sensation is shown moreover by the fact that in many cases of disease the sense of pain may be abolished without the sense of touch. Such a patient is said to suffer from analgesia, but not from *anæsthesia*. When pricked on an analgesic part the patient can say that he is pricked, but has no objection to any amount of repetition of the stimulus, since the sensation is entirely devoid of painful character. In the case of the skin, the sense organs concerned in pain appear to be the free intra-epithelial nerve endings. Pain is found to differ somewhat from the other skin sensations in being much more uniformly distributed, more difficult to locate accurately, and more hardy. Thus

while most sense organs are rendered less sensitive by cutting off blood supply, pain at first reacts more violently.

Protopathic and Epicritic Sensations. As the result of experiments by Head and Rivers, in which a sensory nerve (the radial) in the arm was cut, and the returning sensibility followed during regeneration, it was thought that the sensations could be divided into three groups—epicritic, protopathic and deep. Deep remained after the nerve had been cut, and consisted of pressure sense and pressure pain. Protopathic was the first to return and consisted of a vague pain sense and a sensation to hot objects above 38° C.

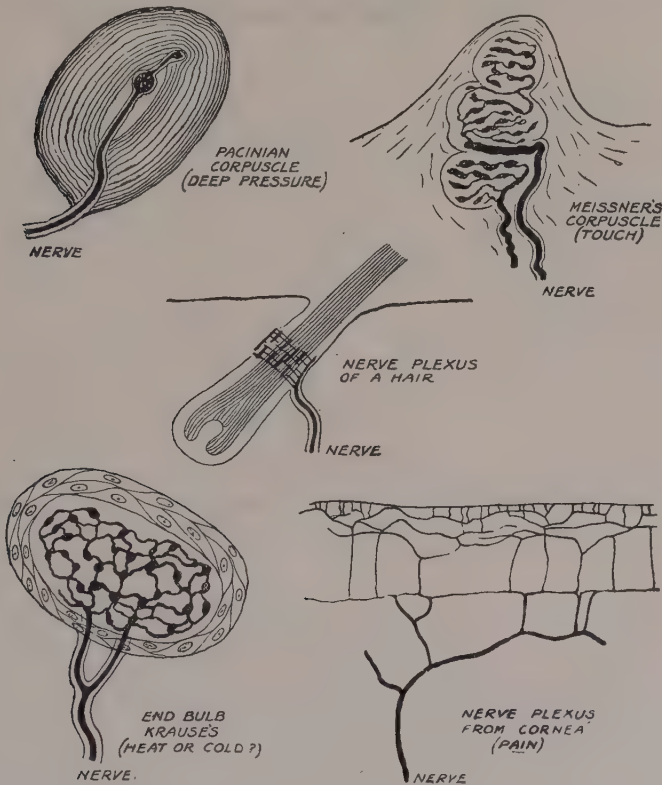


FIG. 274. Skin End Organs and the Sensations which they arouse.

and cold ones below 24° C. Epicritic, the last to return, gave critical discrimination and localisation and differentiation of temperatures between 25° C. and 37° C.

But recent workers, Trotter and Davies (1909), and Boring (1915), who have repeated Head's and Rivers' experiment, and Carr (1916), who subjected Head's and Rivers' own data to analysis, agree in the conclusion that the distinction into protopathic and epicritic is purely artificial and must be finally abandoned.

THE HISTOLOGICAL CHARACTER OF THE ELEMENTS INVOLVED IN CUTANEOUS SENSATIONS

A very large number of different forms of sensory nerve endings have been described in relation to the skin. Their exact allocation among the different cutaneous senses presents considerable difficulties.

As regards touch, two kinds of elements are probably involved. In the first place, the most sensitive tactile apparatus are the follicles of the short hairs. Around these follicles we find a sheaf of nerve fibres, some of which end in the hair papillæ and others form a ring near the level of the openings of the sebaceous glands. The other tactile

end organ is Meissner's corpuscle. The distribution of these in the skin is, however, not dissimilar to that of the power of *discrimination*, with which they may be specially connected. Other end organs, which are supposed to be stimulated by changes of pressure and therefore to be tactile, are the organs of Ruffini which occur in the papillæ of the palm and fingers and, lying more deeply, the elastic tissue spindles as well as the Golgi corpuscles and the Pacinian corpuscles in the subcutaneous tissue.

As regards pain, we know that in the cornea, which possesses only the pain sense, the sensory nerve endings are in the form of branches of axis cylinders among the epithelial cells. Similar free nerve endings occur in the epidermis all over the body, and it is therefore imagined that these have the special function of subserving the pain sense. We have at present no evidence as to the histological character of the organs by which the sensations of heat and cold are aroused.

CHAPTER XXVI

SENSATIONS OF SMELL AND TASTE

EVERY living organism shows a susceptibility, *i.e.* a power of reaction, to chemical stimuli. These movements of attraction and repulsion are spoken of as positive and negative chemiotaxis respectively. The aggregation of leucocytes round microbes or other foreign particles in the tissues is also determined by their chemiotactic sensibility. *Chemiotaxis*, then, represents the faculty by means of which these minute organisms are able to adapt themselves to chemical changes in their environment and to react to chemical substances at a considerable distance from themselves. If we could endow these elementary organisms with consciousness and with a sense of their surroundings, we should have to say that they become aware of the presence of some harmful or attractive material at some distance from themselves. The sensation they receive from these distant objects would be therefore a projected sensation.

On the other hand, a chemical sensibility of the body surface, or part of it, furnishes the criterion by which particles are accepted and ingested as food or rejected as useless or harmful. Consciousness in this case would be of something in contact with and affecting some part of the organism itself. The sensation would not be projected further than the periphery of the body.

These two kinds of chemical sense—the projected and the surface sense—are found throughout almost all classes of the animal kingdom, and in the higher animals at least are known as the senses of smell and taste. The former sense in many animals attains a high degree of complexity and is prepotent in determining the behaviour of an animal in response to the changes in its surroundings. In the elasmobranch fishes the olfactory lobes form the greater part of the higher brain, and extirpation of them produces a loss of spontaneity and of delayed reactions similar to that which can be brought about in higher types by extirpation of the whole of the cerebral hemispheres.

The sense of taste, on the other hand, is used only for sampling the nature of substances taken into the mouth and determining their ingestion or rejection. It is therefore much simpler in its extent and more susceptible of analysis.

THE SENSE OF TASTE

The end organs which subserve the function of taste are represented by the *taste buds*. These are oval bodies (Fig. 275) embedded in the stratified epithelium, which occur scattered over the tongue, a few being also found on the hard palate, the anterior pillars of the fauces, the tonsils, the back of the pharynx, the larynx, and the inner surface of the cheek. On the tongue they are found chiefly in the grooves around the circumvallate papillæ of man, and in the grooves of the papillæ foliæ of rabbits. A few are also present on many of the fungiform papillæ. They consist of medullary and cortical parts, the former being composed of columnar or sustentacular cells, the latter of thin fusiform cells, the taste cells proper. The nerve fibres concerned with taste end

in arborisations among these taste cells. The peripheral end of the fusiform cell projects as a delicate process through the orifice of the taste bud, so that it can come in contact with the fluids contained in the cavity of the mouth. A sapid substance, to stimulate these organs, must be in solution; hence quinine in powder is almost tasteless, owing to its slight solubility.

DIFFERENTIATION OF TASTE. The number of different tastes is very limited. We distinguish four primitive taste sensations, viz. sweet, sour, bitter and salt, some authors adding to these an alkaline taste and a metallic taste. Many substances owe their distinctive character when taken into

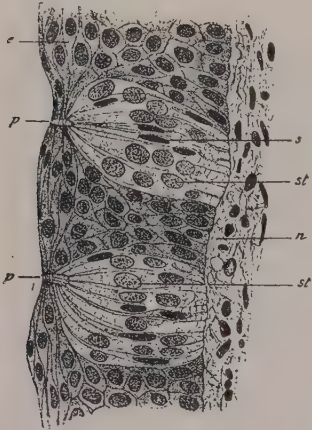


FIG. 275. Two Taste Buds from the Tongue. (KÖLLIKER.)

- e.* Stratified epithelium.
- p.* Opening or pore of taste bud.
- s.* Gustatory cells.
- st.* Sustentacular cells.

the mouth to the fact that they stimulate not only the taste nerves but also the nerve endings of common sensation. Thus acids, when in weak solution, have an astringent character besides their sour taste, and if strong produce a burning sensation. The primitive taste sensations can affect one another if excited simultaneously. With weak stimulation one taste may practically annul another. Thus a dilute solution of sugar is rendered almost tasteless by the addition to it of a few grains of common salt. If the primitive taste sensations are more strongly excited we get a mixed sensation, in which the components can still be distinguished. Thus, adding sugar to lemon juice not only diminishes its acidity but produces a mixed sensation, the quality of which is pleasant and in which the components, sour and sweet, can be easily distinguished. We get no such fusing of sensations as in the eye, where a sensation of white light may result from stimulation of the retina by two complementary colours. Stimulation of one kind of taste organ heightens the sensibility of the other taste organs. Thus after the application of salt, distilled water may taste sweet. The sense of taste may be investigated in three ways: (1) By ascertaining the greatest dilution of a substance that will cause a definite taste, (2) by ascertaining how long a solution of a substance must be applied for a taste to be aroused, (3) by ascertaining the least difference between the strengths of two solutions of the same substance which taste different to the experimenter.

By these methods we find:—

(a) The tongue is not equally sensitive at all points to all four tastes. Thus the back of the tongue is more sensitive to bitter, while the tip and sides of the tongue react more easily to sweet and sour substances. A difference may even be detected between the circumvallate papillæ themselves; a mixture of quinine and sugar applied to one papilla may excite chiefly a bitter taste, while with an adjacent papilla a sweet taste may predominate.

(b) By certain drugs we can depress the sensibility of the taste organs, and we then find that the various tastes are affected to different degrees. Thus on painting the tongue with cocaine the first effect is a diminution of tactile and pain sensibility, so that the application of acid evokes a very sour taste without any of the astringent or stinging sensations normally aroused by the contact with the acid. After this point the taste sensations are also abolished. The bitter sensation disappears first, then the sweet

and then the sour, while the taste of salt appears to remain unaffected. On the other hand, if the leaves of *Gymnema sylvestre* be chewed, the sensations of bitter and sweet are abolished, leaving intact the acid and salt tastes, and also the general sensibility of the mucous membrane.

TASTE AND CHEMICAL CONSTITUTION. There is no doubt that the stimulating effect of any chemical substance on the taste nerves has relation to its chemical constitution. Thus a sour taste is determined by the presence of H ions; the alkaline taste by that of OH ions. The fact that certain acids, *e.g.* acetic, have a stronger sour taste than would correspond to their dissociation, *i.e.* to the number of H ions present, is due to the fact that these acids penetrate more easily into the gustatory cells than the mineral acids with a larger dissociation co-efficient. All the α -amino-acids have a sweet taste. On the other hand, the polypeptides produced by the combination of these amino-acids, as well as the peptones derived from the hydrolysis of proteins, have a bitter taste. Most of the alcohols and sugars have a sweet

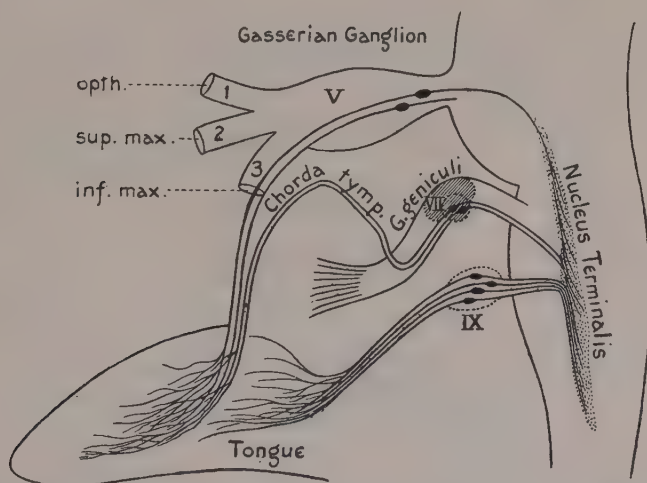


FIG. 276. Diagram showing Origin and Course of the Nerve Fibres of Taste.

taste, while the metallic derivatives of these substances are bitter. We do not yet understand the law which determines whether any given substance shall have a taste at all, and what its taste should be.

The nerves of taste are the glossopharyngeal, which supplies the back part of the tongue, and the lingual branch of the fifth nerve and the chorda tympani which supply the front part. All these fibres are probably connected with a continuous column of grey matter in the brain stem, which represents the splanchnic afferent nucleus of the fifth nerve, the nervus intermedius and the glossopharyngeal. Some authors have stated that all the taste fibres of the fifth nerve are derived from the glossopharyngeal by the communication through the tympanic plexus and the chorda tympani nerve, while Gowers has recorded a case of complete unilateral loss of taste in which there was a lesion destroying the fifth nerve, the glossopharyngeal being intact. It seems possible that the actual region of the taste nerve may vary, the fibres running to the splanchnic column of grey matter being contained sometimes in the fifth, sometimes in the glossopharyngeal, and sometimes in both.

Most of our so-called tastes should rather be designated flavours and

are dependent not on the gustatory nerves but on the sense of smell. When the olfactory sense is destroyed, very little difference is to be perceived between an onion and an apple. The epicure with a fine palate has really educated his sense of smell and would be but little satisfied with the simple sensations derived from his tongue.

✓ THE SENSE OF SMELL

The analysis of olfactory sensations is rendered difficult by the fact that this sense in man plays but a small part in his usual adaptations. We have thus to deal with a sense which is in many respects vestigial. We see traces of great complexity in its possibilities of performance, but are baffled in our endeavours to reduce the whole of the phenomena to the

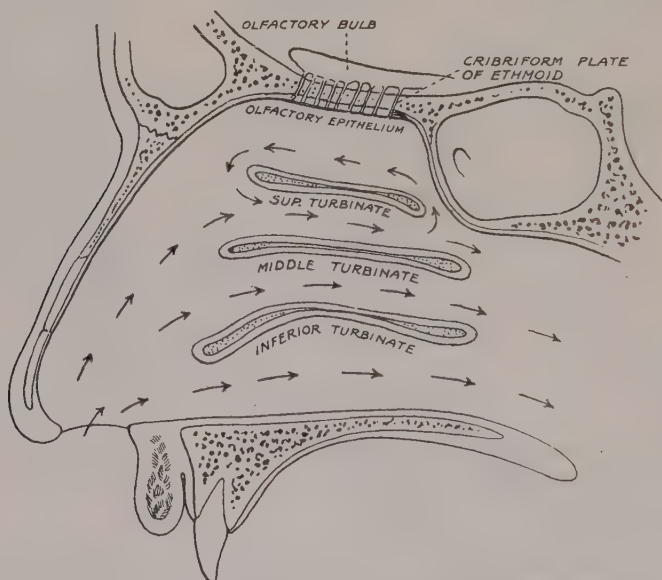


FIG. 277. Antero-posterior Section through the Nasal Fossae. The arrows show the direction of the air currents during inspiration.

simpler factors of which they are composed. Moreover, like all vestigial functions, the extent to which the sense is developed varies from one individual to another. Many, for instance, are unable to appreciate the smell of vanilla, of hydrocyanic acid or of violets. On the other hand, in animals such as the dog, the olfactory sense seems to play a great part in determining behaviour, and the nervous associations, which are the physiological basis of ideas, must in these animals be largely connected with olfactory impressions. Another factor which diminishes the importance of olfactory sensations in man is the ease with which the sense organ becomes fatigued. It often happens that the inmates of a room are perfectly comfortable and may perceive no fault in the ventilation, although a newcomer from the outside at once remarks that the air is foul.

THE ORGAN OF SMELL is situated at the upper part of the nasal cavities. Here the mucous membrane covering the superior and middle turbinate bones and the corresponding part of the septum is different from that covering the rest of the nasal passages. Over the lower parts of the nasal cavities the mucous membrane is of the

ordinary respiratory type, and is composed of ciliated columnar epithelium containing a number of goblet cells. In the olfactory part the epithelium is much thicker, of a yellow colour, and apparently composed of a layer of columnar cells resting on several layers of nuclei. These nuclei belong to the olfactory cells proper, true spindle-shaped nerve cells with one process extending towards the mucus covering the free surface, while the other is continued along channels in the bone, and through the cribriform plate as one of the non-medullated olfactory nerve fibres. These nerve fibres dip into the olfactory lobes, where they terminate by a much-branched arborisation or end basket in the so-called olfactory glomeruli, in close connection with a similarly branched dendrite of the large *mitral* cells of the olfactory lobe. The axons from these latter carry the olfactory impulse towards the rest of the brain. In the connective tissue basis (dermis) of the mucous membrane are a number of small serous glands (Bowman's glands) whose office it is to keep the surface of the membrane constantly moist.

In ordinary respiration the stream of air never passes higher than the anterior inferior border of the superior turbinate bone, so that it does not come in contact with the olfactory mucous membrane. The sensations of smell which are aroused during ordinary respiration depend on diffusion from the respiratory air into the still air of the upper olfactory portion of the nasal cavity. The direction of olfactory attention is achieved by sniffing; in this act the nostrils are dilated and the direction of the anterior part of the nasal respiratory chamber altered, so that the stream of entering air is directed towards the upper olfactory portion of the cavity.

The fact that the air, which enters the nasal cavity during respiration, does not come into direct relationship with the olfactory epithelium has the following advantages:

(1) The cold inspired air does not come into contact with and cause damage to the sensory surface.

(2) Foreign particles carried by the air (including bacteria) do not get deposited there. The position of the epithelium at the very top of the nasal cavity is an additional safeguard.

(3) The olfactory epithelium is not dried by the rush of dry air across it.

(4) Noxious vapours only reach it indirectly and therefore do not cause permanent damage as they otherwise might.

The amount of substance necessary to excite sensation is extremely minute. Thus 0.01 mg. of mercaptan diffused in 230 cubic metres of air is still distinctly perceptible. In this case a litre of air would contain only 0.00000004 mg. of the substance, and the amount actually in contact with the olfactory epithelium would be still smaller. It is possible, however, to show the presence of these odorous substances in air by physical means. Tyndall pointed out that air containing a small proportion of odorous substances absorbed radiant heat to a much greater degree than did pure air. Thus in one experiment, air containing patchouli absorbed radiant heat thirty-two times as strongly as the pure air. Most odorous substances possess large molecules and have therefore high vapour densities. On this account the smell tends to hang about objects, the rate of diffusion of the vapour being only small.

MODE OF ACTION OF ODOURS. Since the endings of the olfactory cells are bathed in fluid, it is evident that the odorous substances must be dissolved by this fluid before they can excite the olfactory nerve fibres, and in the case of aquatic animals we know that the projected chemical sense, which we call smell, can be aroused only by substances in solution. It is difficult to show in man that the nerve endings can be excited by solutions. Most of the experiments have been made with solutions which had an injurious effect upon the olfactory epithelium. According to Aronsohn it is possible to excite sensations of smell, if the nasal cavity be filled with normal saline fluid containing a very small proportion of the odorous substance. To this

experiment it has been objected that it is almost impossible to fill the nasal cavities without leaving some air spaces, so that the olfactory sensation obtained might have been due to stimulation of the olfactory cells in such a space. There is, however, no *a priori* reason to deny the probability of Aronsohn's conclusions. *(I am the cause of the.)*

Many olfactory stimuli owe their peculiar character to the simultaneous stimulation of other kinds of nerve endings. Thus a pungent smell, as that of ammonia, chlorine, &c., besides stimulation of the olfactory nerve, involves stimulation of the nerve endings of common sensibility, supplied by the fifth nerve.

No satisfactory classification of smells has yet been made. The following facts tend to show that there are a number of primitive sensations of smell, as of other sensations :

(a) Certain individuals, whose olfactory sense is in other respects normal, have no power of distinguishing some odours.

(b) The olfactory sense is easily fatigued. If it be fatigued so as to be absolutely insensitive for one kind of smell, it is still normally excitable for other smells.

(c) It is possible by mixing odoriferous substances in certain proportions to annul their effect on the olfactory organ. Thus 4 grm. of iodoform in 200 grm. of Peruvian balsam is almost odourless, and the same neutralisation of odours is obtained if the odour of each substance be allowed to act separately on each side by tubes inserted into each nostril.

BOOK IV
NUTRITION

CHAPTER XXVII

THE EXCHANGES OF MATTER AND ENERGY IN THE BODY

ALL the energy which leaves the body as heat or work is derived from processes of oxidation, the carbon, hydrogen, nitrogen and sulphur of the foodstuffs being oxidised and eliminated in the form of carbon dioxide, water, urea and allied substances, and sulphates. In a starving animal this discharge of energy must be associated with a loss of body substance. The necessity for taking food is determined by the need of replacing this loss. Many foodstuffs cannot, like the coal or fuel of a steam-engine, be utilised directly as a source of energy, but must be built up to a greater or less degree into the structure of the living protoplasm. The total amount of living material in the body, though maintained fairly constant in the adult animal, may yet undergo alterations under varying conditions, and these alterations are naturally more marked in the growing animal. We have in this chapter to inquire into :

- (1) The nature and amounts of the substances which serve as foodstuffs and are necessary for maintaining the weight of the body constant or providing for its growth ;

- (2) The relation between the total amount of material taken up by the body and the total amount given out ;

- (3) The variations in the total chemical exchanges determined by variations in the output of energy by the body ; and

- (4) The significance of the various classes of foodstuffs as sources of energy and in the replacing of tissue waste.

We have therefore to make balance sheets of two kinds, namely : (1) an accurate comparison of the ingesta (food and oxygen) and the egesta (carbon dioxide, water, urea, &c.) ; and (2) one showing the amount of potential energy introduced into the body compared with the amount of energy set free in the body.

METHODS EMPLOYED IN DETERMINING THE TOTAL EXCHANGES OF THE BODY

The determination of the material exchanges of the body involves an accurate comparison of its income and output. The income consists of the foodstuffs and oxygen. The foodstuffs may be divided into two classes, namely, (1) the organic foodstuffs, which on oxidation may serve as sources of energy, and (2) the inorganic foodstuffs, such as salts and water.

The latter class neither add to nor subtract from the total energy of the organism, but their presence is a necessary condition of all vital processes ; and as they are contained in the various excreta, a corresponding amount must be present in the food in order to make good this loss.

In spite of the bewildering complexity of the nature of the foods taken

by man, their essential constituents can usually be assigned to the three classes, proteins, fats and carbohydrates; and any analysis of the food must give the relative amounts present of these three classes of substances. The proximate analysis of the foodstuffs presents little difficulty. The nitrogen is determined by Kjeldahl's method. The figure thus obtained is multiplied by the factor 6.25, and the resulting figure is taken to represent the total protein in the food. Of course such a valuation may give too high a value when the foodstuff is one that is rich in nitrogenous extractives. The total fat is determined by extracting the dried food in a Soxhlet apparatus with ether. The total ethereal extract obtained is reckoned as fat. The amount of water is determined by drying the foodstuffs at 105° C., and the amount of inorganic constituents by ashing the dried remainder. Carbohydrates may be determined directly by boiling the food with dilute acids in order to convert all its disaccharides and polysaccharides into hexoses, which are then estimated by their copper-reducing power, and reckoned as glucose. In some cases, however, the total protein, fat and ash are subtracted from the dried weight of the food and the remainder is taken as carbohydrate.

The labour of the very large number of analyses which have to be performed is lightened by the fact that nearly all the ordinary foodstuffs have been subjected to analysis and their average composition published.* Since, however, the foods vary in composition, especially in water content, from time to time, a calculation of the total income of proteins, fats and carbohydrates from data given by workers in other lands must present a considerable margin of error. In order to attain greater accuracy, some observers have made a complete food in the form of biscuits or of preserve, which is prepared in large quantities at the beginning of the experiment and used as the sole diet throughout the experiment. Pflüger, for instance, converted the horse-flesh, with which he desired to feed his dogs in a metabolism experiment, into sausage meat which was sealed up in cases and sterilised. The sausage meat having been analysed at the beginning of the experiment, it was only necessary thereafter to weigh the amount eaten by the dog in order to know accurately the total amount of protein, fat and carbohydrate ingested by the animal. In experiments on man it has been endeavoured to obtain the same result by limiting the food to a few articles of diet which could in each case be accurately analysed. The monotony of such a diet tends to interfere with the success of the experiment, since the subject loses his appetite and his processes of nutrition are not normally carried out. It is usually possible to steer a middle course between the two extremes, and so to obtain values for the composition of the ingesta which cannot differ very largely from their true composition.

The material output of the body is turned out by the various channels of excretion, namely the kidneys, the alimentary canal, the lungs and the skin. These excreta must therefore be collected and analysed. In addition to the main sources of excretion, small quantities of material are lost by the shedding of the cuticle, by the growth and cutting of the hair and nails, and so on. In most cases the losses in this way are so small that they may be disregarded. The nitrogen of the foodstuffs and that derived from the disintegration of the tissues of the body is excreted almost exclusively in the urine, a small amount being thrown out by the alimentary canal. The total nitrogen must therefore be determined both in the fæces and in the urine. The nitrogen in the fæces is derived from two sources. Part represents those nitrogenous constituents of the diet which have resisted the digestive processes of the alimentary canal. There is in addition a certain amount derived from the intestine itself. Even during complete starvation faecal masses are formed in the intestine, and it has been calculated that in a normal individual about 1 gramme of nitrogen a day is excreted by the mucous membrane of the gut and contributes to the formation of the fæces. It is usual, therefore, in

* R. H. A. Plimmer, "Analysis and Energy Values of Foods," H.M. Stationery Office, 1921. Atwater and Bryant, Bull. 28, U.S. Dept. Agricult., 1906.

experiments on man, to regard 1 gramme of the nitrogen of the fæces as belonging to the *output* of the body and representing the result of nitrogenous metabolism, while the balance is taken as belonging to undigested foodstuffs, and is subtracted from the total nitrogen of the latter in reckoning the real *income* of the body.

A small amount of nitrogen is also lost by sweat, but this can be disregarded unless the sweating is profuse, when the loss of nitrogen by this channel may rise to as much as 4 per cent. of the total nitrogenous output of the body. Although a trace of ammonia has been described as occurring in the expired air, this possibly arises by bacterial action in the mouth. However, the amount is so minute that this loss of nitrogen can be neglected. That the loss by both lungs and skin under ordinary circumstances can be disregarded, is shown by the fact that it is possible to account directly for the whole nitrogen of the body by a comparison of the composition of the food with that of the urine and fæces. If, for instance, an animal is kept on a sufficient diet which contains a regular amount of nitrogen, after a few days a condition known as *nitrogenous equilibrium* is set up, *i.e.* the total nitrogen of fæces and urine is exactly equal to the total nitrogen of the food. The same applies to the sulphur, as shown in the following Table (quoted by Tigerstedt):

Days of experiment.	Nitrogen of food.	Nitrogen excreted.	Per cent. difference.	Sulphur ingested.	Sulphur excreted.
1-7	154.81	153.02	- 0.51	—	—
8-17	213.72	213.26	- 0.21	12.77	12.79

In order to express the nitrogenous metabolism in terms of protein, we use the factor employed in estimating the amount of protein in the food, *i.e.* we multiply the total nitrogen of the excreta by 6.25. This will give the total protein which has been broken down during the period of the experiment.

Much more important from the energy standpoint is the determination of the total processes of oxidation of the body, information on which is given by a determination of the oxygen intake and of the output of carbon dioxide and water. The estimation of these substances presents greater difficulties than the investigation of the nitrogenous exchange, and involves the use of some form of respiration apparatus.

The methods which have been used for this purpose are very numerous, but are of two main types, the closed or re-breathing type and the open or expired-air-analysis type. In the closed type, the subject breathes an atmosphere which circulates in a closed apparatus; the carbon dioxide produced is absorbed and weighed, and oxygen is added in measured amount to keep the volume of the enclosed atmosphere constant: the nitrogen is breathed over and over again. In the open type fresh air is inspired, and the expired air is subjected to measurement and analysis in one of several ways. The Regnault and Reiset apparatus is on the closed principle; Haldane's, Zuntz's and Douglas' methods are on the open principle.

I. THE METHOD OF REGNAULT AND REISET. The animal that is to be the subject of investigation is placed in a closed chamber containing a given volume of air. The carbon dioxide produced by the animal is absorbed by means of caustic alkali, and the oxygen consumed by the animal is made good by allowing oxygen to flow into the chamber from a gasometer. The inflow of oxygen is regulated so as to keep the pressure of air in the chamber constant. At the end of the experiment, the alkali is titrated or weighed, and the amount of carbon dioxide absorbed thus determined. The air in the chamber is also analysed so as to be certain that it contains an excess neither of carbon dioxide nor of oxygen. The amount of oxygen absorbed by

the animal is known already, the oxygen which has been allowed to flow in having been measured.

A modification of this method has been devised by Benedict and is especially applicable to clinical purposes. In this method, the subject of the experiment

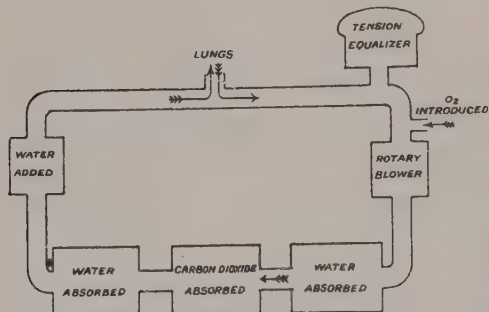


FIG. 278. Air Circuit in Benedict's Respiration Apparatus.

nose-piece for breathing, the tension equaliser, the air-purifying apparatus, and the oxygen cylinder. The tension equaliser, A, is attached to the ventilating pipe near the point of entrance of the air into the lungs. It consists of a pan with a rubber diaphragm (which may be conveniently made from a lady's bathing-cap). As the air is drawn into the lungs the rubber diaphragm sinks, to rise again with expiration. The respiratory movements can thus proceed without appreciably altering the pressure within the closed system of tubes. By the admission of oxygen the supply of oxygen is adjusted so as to keep the bag from becoming either too much distended or too much flattened. As the air leaves the lungs and is swept into the constantly moving current of air, it is carried along by the pump and flows through two Wolf's bottles containing strong sulphuric acid and pumice for the removal of water vapour. It then passes through a brass cylinder, C, filled with soda lime for the absorption of carbon dioxide. From here it passes again through sulphuric acid in a Kipp generator for the absorption of water given off by the soda lime. Since the air so deprived of moisture would be uncomfortable to breathe, it is then carried through another Kipp generator containing water with a trace of sodium carbonate for the neutralisation of any acid fumes which may be given off by the sulphuric acid. It then passes back to the tube from which the subject is breathing. In this way it is possible to determine very accurately the amount of oxygen used up, and the amount of carbon dioxide given off, in the course of an experiment lasting one to three hours, or longer. The oxygen consumption is measured by weighing the cylinder of this gas, chosen small for this purpose, before and after the experiment, or else by running it in through a meter.

The Atwater-Benedict Respiration Calorimeter, on a similar principle, is described on p. 504.

II. THE KROGH SPIROMETER. This simple modification of the closed

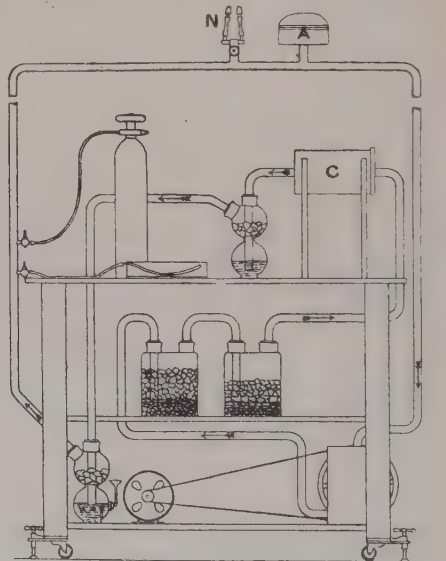


FIG. 279. Arrangement of Apparatus in Benedict's Method for Determination of Respiratory Exchange.

N. Tubes inserted into nostrils of patient.

A. Tension equaliser.

C. Cylinder containing soda lime for absorbing CO_2 .

method is convenient for short periods. The subject breathes in and out of a mouth-piece connected by valves with a recording tank spirometer (Fig. 280) containing soda-lime. As oxygen is used, the respiratory record is written on a sloping base line; more oxygen is added through a gas meter from time to time to restore the respiratory base line. The rate of oxygen usage at any time is given by the slope of the respiratory tracing. A modification of the arrangement by Dusser de Barenne enables the CO_2 also to be determined.

III. THE METHOD OF HALDANE. This method is extremely convenient when dealing with the gaseous exchanges of small animals, such as mice, rats, or

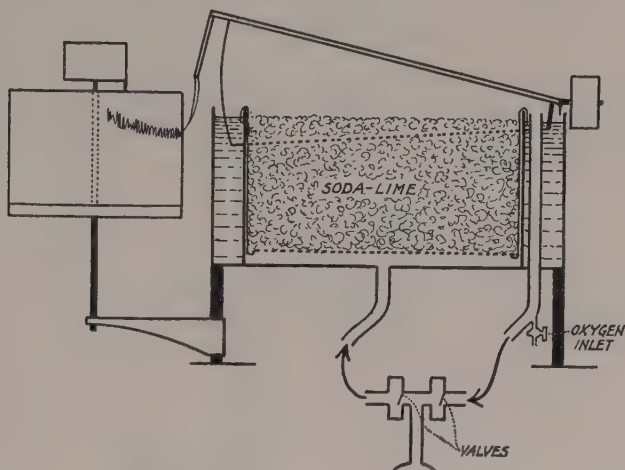


FIG. 280. Krogh's Recording Spirometer.

frogs. The animal is placed in the chamber C, which may be simply a wide-mouthed bottle (Fig. 281). This chamber is supplied with a thermometer, and can be kept at any desired temperature by immersion in a water-bath. On the inlet side of the bottle is a series of tubes or bottles, some of which contain sulphuric acid and pumice stone, while the others contain soda lime. On the outlet side of the vessel is a corresponding series of vessels for the absorption of water and of carbon dioxide. On the further side of these vessels is a gas meter. During an experiment air is sucked through the whole apparatus by means of an aspirator or a water pump, the amount of air passing through the apparatus being measured by the meter. The

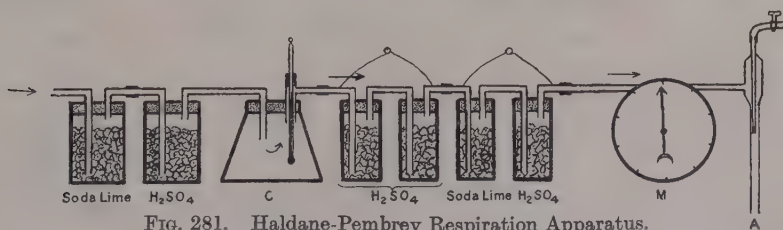


FIG. 281. Haldane-Pembrey Respiration Apparatus.
C. Chamber for animal. M. Gas meter.

animal is thus supplied with pure air freed from water vapour and from carbon dioxide. All water or carbon dioxide produced by the animal is absorbed by the vessels interposed on the course of the outgoing air. These vessels are weighed at the beginning and at the end of the experiment, and the difference in weights will therefore give the amounts of carbon dioxide and water which have been discharged by the animal.

The intake of oxygen by the animal is determined indirectly. Since it gives off only carbon dioxide and water, and absorbs only oxygen during its stay in the chamber, the loss of weight of the animal during its stay in the chamber, subtracted from the total weight of carbon dioxide plus water it gives off, will represent the weight of oxygen absorbed.

The advantage of this apparatus is that it can be fitted up in any laboratory, and

is accurate for the purposes to which it is applied. It is not, however, appropriate for long-continued experiments, or for experiments on larger animals or on man himself, though Pettenkofer did design a human respiratory chamber of about 100 cubic metres capacity, on similar lines, the ingoing and outgoing air being both measured and analysed. The experimental error is large. Most of the data with regard to the respiratory exchange under various circumstances have therefore been obtained by one of the following methods.

IV. ZUNTZ AND GEPPERT'S METHODS. For many purposes the method devised by Zuntz and Geppert presents advantages for a limited period of time. The subject of the experiment has his nostrils clamped and breathes into and out of a face-piece. This face-piece is provided with valves which serve to separate the in-going from the out-going current of air. In the course of the out-going current is placed a very delicate gas meter. A branch from the efflux tube passes to a gas analysis apparatus. By an ingenious arrangement, an aliquot part of the whole of the out-going air is drawn off into this apparatus, so that the experiment can be interrupted at any time, and the analysis of this sample will give the average composition of the expired air and therefore, on multiplication by the total gas passing through

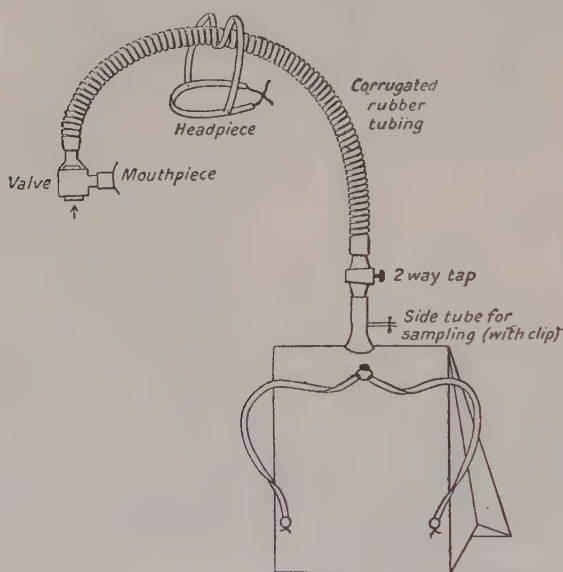


FIG. 282. Douglas' Bag for Determining Respiratory Exchange in Man.

the gas meter, the total exchange during the course of the observation. One advantage of this method is that the apparatus is portable.

V. THE DOUGLAS BAG. By far the most convenient method for estimating the respiratory exchanges of man under varying conditions is by the use of the Douglas Bag. The subject for experiment breathes through a mouthpiece provided with valves so arranged that he inspires from the external air and expires into a bag of about 100 litre capacity. After from two to ten minutes the bag is removed, the time being accurately noted. The amount of air expired during this time is measured by emptying the bag through a gas meter. A sample of its contents is analysed and the oxygen and CO_2 in it determined. Since the composition of the external air is known, the analysis and measurement of the expired air gives the respiratory metabolism during the time of the observation. The bag is carried on the back of the individual, so that it does not interfere with his movements. This method has been used for determining the metabolism of soldiers in training, of munition workers, athletes, &c.

CALCULATION OF RESULTS. In the closed circuit methods, the weight or volume of oxygen used and carbon dioxide produced are given directly, and any necessary corrections, *e.g.* of volumes to dry volumes at N.T.P., are obvious. With the open methods, some explanation is necessary. The subject inspires ordinary air which contains 20.96 volumes per cent. of oxygen, 79 per cent. N_2 , and 0.04 per cent. CO_2 , and the

volume and composition of his expired air during a given interval is what is actually determined. As regards CO_2 , let us suppose that the expired air contains 4.10 per cent., i.e. an increase of 4.06 per cent.; then, if his volume of expired air is 8.5 L. per min., the volume of CO_2 expired is $8.5 \times 4.06 \times 10 = 345$ c.c. per minute. The oxygen is less direct because, as explained in Chapter XXXIX., the expired air has a smaller volume than the inspired, the *percentage* of nitrogen being raised owing to utilisation of oxygen which is not converted to CO_2 . The *total amount* of nitrogen breathed out is, however, equal to that inspired. Hence, if the expired air contains, say, 79.5 per cent. N_2 and 16.4 per cent. oxygen, then each 100 c.c. expired air corresponds to $\frac{100 \times 79.5}{79} = 100.6$ c.c.

inspired air and this contained $\frac{20.96 \times 100.6}{100} = 21.09$ c.c. oxygen, so that the oxygen utilised per minute was $(21.09 - 16.4) \times 85 = 398$ c.c.

The *Respiratory Quotient* is obtained, when required, from the respiratory exchange. It is the ratio of the volume of carbon dioxide produced during a given time to the volume of oxygen utilised during the same time. In the above example it is $\frac{345}{398} = 0.87$.

By these methods we may arrive at a correct idea of the total income and output of an individual for periods up to many days. The following details by Tigerstedt may serve as an example of the results obtained in such an experiment. The experiment lasted two days. The subject was a man of twenty-six years of age, weighing about 65 kilos., who had previously taken no food for five days. The following Tables represent his material income and output.*

TOTAL INCOME

Food.	Total amount.	N.	O.	Water.	Solids.	Protein.	Fat.	Carbo-hydrate.	Ash.	Alcohol.
Bread . . .	373	7.3		36	337	46	4	278	9	—
Butter . . .	388	0.4		37	351	3	337	4	7	—
Cheese . . .	116	4.3		56	60	27	35	—	5	—
Salt meat . . .	26	1.1		16	10	9	—	—	2	—
Milk . . .	2313	11.3		2047	266	71	85	95	16	—
Broth . . .	658	11.8		580	78	74	—	—	9	—
Beer . . .	1413	1.2		1273	77	8	—	67	3	59
Beef steak . . .	700	20.6		533	167	129	33	—	7	—
Potatoes . . .	452	0.9		359	93	6	1	82	5	—
Water . . .	2335	—		2335	—	—	—	—	—	—
Totals . . .	8773	59.3	831.6	7275	1439	371	497	525	61	59

TOTAL OUTPUT

	Total amount.	N.	O.	Water.	Solids.	Protein.	Fat.	Carbo-hydrate.	Ash.
Respiration .	2701	—	453.0	2248	—	—	—	—	—
Urine . . .	2564	41.5	32.5	2490	—	—	—	—	21
Fæces . . .	455	4.8	43.8	363	91.6	30	20	27	15
Totals . . .	5720	46.3	529.3	5101	91.6	30	20	27	36

* Fractions are omitted except in case of N, but are included in the totals. Carbon is reckoned by difference.

As we should expect in a man who had previously fasted five days, this balance sheet shows a marked retention of the food taken in, *i.e.* a marked excess of income over output. Thus of the nitrogen ingested, 13 grammes, which is equivalent to 81.3 grammes of protein, was retained; of the carbon, 302 grammes was retained. Of this 302 grammes, 42.7 grammes would be contained in the 81.3 grammes of protein, so that the rest of the carbon, namely, 259.6 grammes, was probably laid down in the form of fat. This would correspond to 339 grammes of fat. Of the salts contained in the ash of the food, 25 grammes were retained in the body. The carbon and nitrogen reappearing in the excreta serve as an index of the amount of metabolism of the foodstuffs which had occurred during the two days. In order to supply the energy requirements of the body during the time of the experiment, 498 grammes of carbohydrate, 59 grammes of alcohol, and 138 grammes of fat had been completely oxidised. The amount of protein used up during this time can be obtained by multiplying the nitrogen of the urine plus 1 gramme of nitrogen of the fæces by the factor 6.25, and is found to amount to 271.9 grammes.

THE ENERGY BALANCE SHEET OF THE BODY

The energy income of the body is measured by the potential energy of the foodstuffs, *i.e.* the amount of energy which can be evolved, either as heat, work or in any other form, by the oxidation of the foodstuffs to the end products which occur in the body. We generally express the total potential energy of a foodstuff in *Calories*. The heat value of any given food is the number of large Calories * which it evolves on complete combustion with oxygen, and is determined by burning a weighed quantity of the dried foodstuff in oxygen in the bomb calorimeter. The following heat values have been obtained for different foodstuffs:

Substance.	Heat value. (Calories.)
Lean meat	5.656 (or 5.345 Rubner)
Lard	9.423
Butter	9.231
Glucose	3.692
Cane sugar	4.116
Starch	4.191

In the case of some foodstuffs it is necessary to draw a distinction between the heat value on actual combustion, and the physiological heat value. Since carbohydrates and fats undergo complete oxidation in the body to carbonic acid and water, their physiological heat values, *i.e.* the values of these foodstuffs to the organism, are identical with their absolute heat values. When proteins are oxidised in the bomb calorimeter, the nitrogen is set free in a gaseous form. In the animal body no nitrogen is eliminated in the gaseous form, the whole of it being excreted as urea and allied substances still endowed with a considerable store of potential energy, which can be set free when their oxidation is completed in a calorimeter. In order to determine the physiological heat value of protein, we must subtract from its absolute heat value the heat value of the excretory products in the form of which it leaves the body. The physiological heat value of proteins has been determined by Rubner in the following way: A dog was fed with the same protein which had served for the determination of the absolute heat value, and its urine was collected, dried, and its heat value determined by combustion in the

* A calorie is the amount of heat necessary to raise a gramme of water from 15° C. to 16° C. A large Calorie (printed with a capital C) is the heat required to raise a kilogramme of water from 15° C. to 16° C., and is therefore equal to 1000 small calories.

calorimeter. It was found that, for each gramme of protein which had undergone disintegration in the body, an amount of urine was passed corresponding to a heat value of 1.0945 Calories. The heat value of the fæces formed under the same diet was 0.1854 Calorie for each gramme of protein. Rubner further reckoned that a certain amount of heat would be required for the solution of the proteins and of the urea, and reckoned this at 0.05 Calorie. The reduced or physiological heat value of protein is therefore equal to $5.345 - (1.0945 + 0.1854 + 0.05) = 4.015$ Calories.

Owing to minute differences between individual members of the same class, it is impossible to reckon out accurately the relative values of the different kinds of protein, carbohydrate, &c., contained in each diet, and Rubner has calculated the *average* physiological heat values of the three classes of foodstuffs, and found them as follows :

1 grm. protein	= 4.1 Calories
1 grm. fat	= 9.3 "
1 grm. carbohydrate	= 4.1 "

These figures are accurate only for a diet containing the normal proportion of vegetable to animal foods—60 to 40. The heat value of vegetable protein is as a rule less than that of animal protein. Taking the normal mixture of foods used in civilised countries, the following figures give more accurately the energy available from any given diet (allowing for the loss in digestion) :

Carbohydrates.	Proteins.	Fats.
4 Calories per gramme	4 Calories per gramme	8.9 Calories per gramme

Careful experiments have shown that the sum of the energies put out by the body is equal to the sum of the energy obtained by the oxidation of the tissues and of the foodstuffs in the body during the same time. In an earlier chapter the results of an experiment by Rubner on a dog were quoted as proving the important fact that the fundamental doctrine of the conservation of energy applies to the organised world. Similar results have been arrived at by Atwater in a series of experiments on man. Here are the figures from one such experiment :

Date.	(a) Heat of combustion of food eaten.	(b) Heat of combustion of fæces.	(c) Heat of combustion of urine.	(d) Estimated heat of combustion of protein gained (+) or lost (-).	(e) Estimated heat of combustion of fat gained (+) or lost (-).	(f) Estimated energy of material oxidised in the body; a - (b + c + d + e)	(g) Heat determined.	(h) Heat determined greater (+) or less (-) than estimated: g - f.	(i) Heat determined greater (+) or less (-) than estimated: h ÷ f.
	Cals.	Cals.	Cals.	Cals.	Cals.	Cals.	Cals.	Cals.	%
Dec. 9-10	2519	110	142	- 85	+ 3	2349	2414	+ 65	+ 2.8
10-11	2519	110	133	- 25	- 44	2345	2386	+ 41	+ 1.7
11-12	2519	110	132	- 21	- 93	2391	2413	+ 22	+ 0.9
12-13	2519	110	133	- 14	- 55	2345	2375	+ 30	+ 1.3
Total 4 days	10,076	440	540	- 145	- 189	9430	9588	+ 158	
Average one day	2519	110	135	- 36	- 47	2357	2397	+ 40	+ 1.7

If we take into account the great difficulties of such an experiment, we cannot but be impressed with the closeness of agreement between the total output of energy, reckoned as heat and measured by the warming of a given volume of water, and the total income of energy, as estimated from the chemical reactions involved in the metabolic changes which had taken place during the four days of experiment.

THE RESPIRATION CALORIMETER.—The Atwater respiration calorimeter, as improved by Benedict and his fellow workers, consists of a room or chamber with double non-conducting walls. All round the inner wall of the room are fitted coils of pipes through which a stream of water flows. The pipes are fitted with discs in order rapidly to take up heat produced in the room. The current of water is accurately adjusted so as to maintain the temperature of the inner wall constant. As the inner wall and outer wall are kept at the same temperature, no heat is lost to the exterior, the whole of the heat produced by the animal or individual in the chamber being communicated to the water passing through the cham-

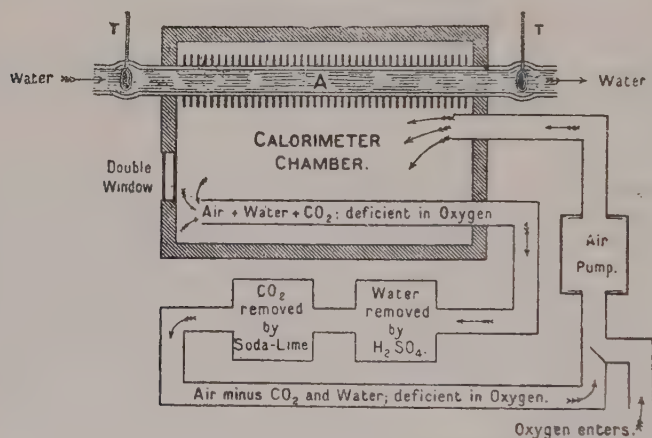
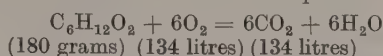


FIG. 283. Diagram to show the Principle of the Atwater-Benedict Calorimeter. (After HALLIBURTON.)

ber. The temperatures of the entering and leaving water are taken by thermometers reading to a thousandth of a degree Centigrade. Knowing the amount of water that has passed through in a given time and the difference in temperature during the same time, it is easy to calculate the amount of heat given off by the animal under investigation. It is generally convenient to maintain a constant difference of temperature between the entering and leaving water, by appropriate adjustment of the amount of water passing through the apparatus. The equality of temperature between the inner and outer casing is recorded by electric thermo-couples, any difference of temperature being at once compensated by electrically warming the cooler part. The chamber contains a bicycle or other arrangement for the performance of mechanical work. It is adequately ventilated by a current of air passing through an apparatus similar to that of Benedict, described on p. 498. It is thus possible to estimate simultaneously the total heat production of an individual as well as the respiratory exchange, including both carbon dioxide output and oxygen intake. The general principle of the calorimeter is shown in the diagram (Fig. 283). The calorimeter is also supplied with bed, table, chair, &c., and food can be introduced through a double window so that

an experiment may be continued over two or three days on one and the same individual.

INDIRECT CALORIMETRY. From the equation



and from the observation that 1 gramme of glucose on combustion yields 3.7 Calories of heat, we can deduce that when carbohydrate is being burnt in the body (*i.e.* when the R.Q. = 1.0), the utilisation of each litre of oxygen generates about 5.05 Calories of heat. Similar calculations can be made for the combustion of proteins or fats (4.69), so that in all cases the calorific value of oxygen is in the neighbourhood of 5 Calories per litre, the exact value varying according to the respiratory quotient, as shown in the following table (*v.* also p. 518):

R.Q.	Cal. per litre oxygen.
1.00	5.047
0.90	4.924
0.80	4.801
0.707	4.686

These figures have been obtained by actual comparison between respiratory exchange and calorimeter experiments on man. It is therefore now quite easy, when the oxygen usage and R.Q. are known, to calculate the total energy liberation of the body, and this method of investigation is called indirect calorimetry.

METABOLISM DURING STARVATION

It will tend to simplify our task if we deal first with the results of the experiments which have been made on the metabolic exchanges of animals during starvation, when the whole energy expenditure is derived from the animal's own tissues. It must be remembered that the tissues of an animal comprise two distinct classes. In the first class must be placed the living machinery of the body, largely composed of proteins or their near allies. In the second class are the fatty tissues of the body, which form no part of the ordinary machinery, but function simply as a storehouse of material which can be utilised for the production of energy. In addition to the store of fat there is, in a well-fed animal, a certain reserve of glycogen, deposited in the liver and the muscles. The total amount of glycogen present at any time is generally so small in comparison with the fat of the body that it cannot provide the energy necessary for the maintenance of life during prolonged inanition, although it plays an important part during the first one or two days of starvation.

Contrary to general belief, the condition of an animal which is completely deprived of food is not a painful one. For this statement we have not only evidence from animals, but also that derived from men who have voluntarily or involuntarily been deprived of food for considerable periods. During the first day or two there is a craving for food at meal-times. This often passes off, and during the later portions of the experiment even the desire for food may be entirely absent. As might be expected, the restriction of food is followed by a diminution in the amount of water required. The essential characteristic of the state of inanition is an ever-increasing weakness, accompanied by a strong disinclination to undertake any mental or physical exertion whatsoever. The animal passes its time in a state of sleep or semi-stupor. Especially instructive in this connection are the cases of the so-called professional 'fasting-men,' two of whom, Succi and Cetti, have been subjected to complete metabolic investigation during their starvation. In the case of Succi, who fasted for thirty days, considerable muscular exertion was undertaken on the twelfth and on the twenty-third day of starvation without

any appreciable ill-effects. A strong effort of the will must have been necessary in his case to overcome the automatic instinct to preservation of life by the utmost economy in the expenditure of energy. The pulse rate and the body temperature remain nearly normal until a few days before death, which is ushered in by an increase in the somnolent condition of the animal and by a gradual slowing of respiration and fall of temperature. The urine is naturally diminished, with diminution in the output of urea and in the amount of water consumed. Some fæces are formed, and may be voided during or at the close of the starvation period. In Succi their amount varied from 9.5 to 22 grammes a day and contained from 0.3 to 1.0 gramme nitrogen. On microscopic examination they consisted of an amorphous material enclosing a number of crystals of fatty acids.

During the whole of the starvation period, energy is being used up in the body for the maintenance of its temperature and the vital movements of respiration and circulation, and there is a steady loss of body weight. In experiments on man, the daily loss of weight during the first ten days amounts to between 1 and 1.5 per cent. of the original total weight. This loss of weight does not affect all parts of the body alike. It might be imagined that, since the loss of weight is determined by the using up of the tissues of the body for the production of energy, those organs which are most active should show also the greatest loss of weight. The very reverse of this is the case, as will be seen from the following Table.

PERCENTAGE LOSS OF WEIGHT OF DIFFERENT ORGANS AND TISSUES DURING STARVATION (VOIT)

Tissue.	Percentage loss of weight of fresh tissue.	Percentage loss of dry tissue.
Fat	97	—
Spleen	67	63
Liver	54	57
Testes	40	—
Muscles	31	30
Blood	27	18
Kidneys	26	21
Skin and hairs	21	—
Intestine	18	—
Lungs	18	19
Pancreas	17	—
Heart	3	—
Brain and spinal cord	3	0

Those organs of the body which are most necessary for the maintenance of life, the brain, the heart, the respiratory muscles such as the diaphragm, undergo very little loss of weight. Of the other tissues the fat, which is a mere reserve to provide for such contingencies, is drawn upon first, and during starvation 97 per cent. of the total fat of the body may be consumed. The nitrogen needs of the body during starvation seem to be supplied chiefly at the expense of the muscles and glands, which waste to a very marked degree. The muscles being used simply as reserve material, it is easy to understand the condition of lethargy and muscular inactivity which characterises the state of inanition. During starvation, all tissues of the body undergo a process of slow autolysis or disintegration, giving up the products of this process to the common circulating fluid. The nutritional demands of a tissue are determined by its activity. Hence the active tissues of the

body take up the material set free from all the other cells of the body and so maintain their weight at the expense of all other parts. A similar predominance of the nutrition of active over inactive tissues is to be observed in cases of partial starvation, *i.e.* where the deprivation of food applies only to a single food constituent. Thus Voit, in a series of experiments, fed pigeons on a food which, while normal in all other respects, contained a deficiency of calcium salts. On killing the birds after a certain length of time, it was found that while the bones used in the necessary movements of the animals presented a normal appearance, the others such as the sternum and skull, showed a marked deficiency of lime salts and had undergone a process of rarefaction giving rise to the condition known by pathologists as osteoporosis. Many other instances of the sacrifice of a temporarily useless tissue on behalf of tissue of high physiological value are known. Thus the salmon lays its eggs and undergoes its early development in the fresh water of the upper reaches of rapid streams. An adult salmon leaves the sea in the early summer months in a magnificent state of muscular development, fit to perform the prodigious feats of swimming which are required in order to get it over the rapids of the river which it has to ascend. It takes no food. In the upper reaches of the stream or river there is a growth of the genital glands, ovaries or testes. The whole material for the growth of these large organs is derived from the atrophy of the skeletal muscles. In this case we have the growth of an active tissue at the cost of an inactive one, the activity however being determined, not by the direct call upon it from the environment, but by what we may speak of as the 'physiological habit' of the animal.

The animal organism, in the complete absence of food, deals with the resources of its bodily tissues with the utmost possible economy. The total metabolism therefore sinks rapidly during the first two days of starvation, and then remains practically constant. There is indeed a slight continuous diminution with the fall in body weight, but the total metabolism per kilo body weight till within a day or two before death is a constant quantity. This is shown in the following Table of the output of energy in man during a five days' period of starvation (Tigerstedt) :

METABOLISM DURING STARVATION (MAN)

Day of experiment.	Nitrogen output.	Fat oxidised.	Total Calories.	Calories per kilo. body weight.
1	12.16	204.8	2231	33.3
2	12.85	190.3	2112	32.1
3	13.62	179.9	2032	31.3
4	13.67	176.4	2003	31.3
5	11.44	180.0	1979	31.4

THE METABOLISM OF CARBOHYDRATE, FAT, AND PROTEIN DURING STARVATION

Since during starvation we can regard the whole expenditure of the animal during its period of starvation as occurring at the expense of its capital, it has often been estimated that the chemical capital of the body consisted entirely of proteins and fats. The glycogen metabolism however, during the first day of a period of starvation, may form a considerable fraction of the total metabolism of the body, and can hardly be excluded.

The relative parts played by protein, carbohydrate and fat respectively in the chemical exchanges of a starving animal may be determined in the following way: The amount of protein consumed is given by estimating the total nitrogen of the excreta by Kjeldahl's method and multiplying the result by the factor 6.25. The loss of weight of the body *minus* the protein consumed may be roughly taken as equivalent to the fat *plus* carbohydrate consumption. But this is only a very rough method, since the quantity of water in the tissues may undergo considerable variations, and so affect the total weight of the body. For any accurate results the respiratory exchanges must be measured, including both oxygen intake and carbon dioxide output. After deducting the carbon dioxide due to the combustion of the carbon of the proteins, which does not appear in the urine in combination with nitrogen, the remainder of the carbon dioxide is derived entirely from carbohydrate and fat metabolism. Knowing the respiratory quotient and the total amount of carbohydrate and fat metabolism, it is possible to come to a conclusion as to how much of the carbon dioxide is derived from oxidation of glycogen and how much from the oxidation of fat. A very efficient check on this calculation is furnished if the individual or animal can be placed at the same time in an accurate calorimeter, because a gramme of fat, when converted into carbon dioxide and water, produces more than double the amount of heat which would be evolved by the complete oxidation of glycogen. In Benedict's experiments the heat value of the metabolism calculated by the above method agreed with the heat as actually measured by the calorimeter within 0.5 per cent., whereas if the total carbon of the first day had been reckoned as fat, the discrepancy would have been as high as 5 per cent. in many cases. The influence of glycogen metabolism on that of protein during the first and second days of fasting is shown in the experiments given below:—

	First day.			Second day.		
	Glycogen metabolised.		N. eliminated.	Glycogen metabolised.		N. eliminated.
	Total.	Per kilo.		Total.	Per kilo.	
S.A.B.	181.6	3.15	5.84	29.7	0.52	11.04
S.A.B.	135.3	2.31	10.29	18.1	0.31	11.97
S.A.B.	64.9	1.09	12.24	23.1	0.39	12.45
H.C.K.	165.6	2.33	9.39	44.7	0.64	14.36
H.R.D.	32.8	0.59	13.25	41.6	0.76	13.53

The total metabolism per kilo. body weight very soon attains a constant level. The relative part taken in the production of the total energy by fats and proteins respectively may vary from animal to animal according to the amount of fat available in the body. If the animal previous to the experiment has been receiving a diet rich in protein, the excretion of nitrogen and urea in the urine diminishes rapidly during the first days of starvation. During the first two days, therefore, a considerable proportion of the necessary energy is obtained at the expense of protein. Between the third and fifth day the nitrogenous excretion reaches a minimum, at which point it remains approximately constant until a day or two before death. If the animal has been receiving a diet very poor in protein, the excretion of nitrogen may be low throughout the whole course of the experiment. These facts are illustrated by the curves in Fig. 284, which show the output of urea in three experiments on a dog under different conditions of nutrition. In the first experiment the dog, before the experimental period, had been receiving 2500 grammes of meat daily; in the second it had been receiving 1500 grammes of meat, and in the third only a small quantity, which was not accurately measured. Although there is a great difference between the urea output during the first day of the experiments, the urea output during the sixth to eighth days is identical. These experiments indicate that it is not possible, by giving extra protein in the diet, to provide any large store

of body protein. In many cases, for a few days before death there is a rise of protein metabolism. This rise is synchronous with a practically complete disappearance of fat from the body. The animal now has to supply all its requirements at the expense of the protein tissues, which therefore waste rapidly and account for the increased excretion of nitrogen. This is shown in the following experiment of Rubner on a rabbit :

Days.	Average daily output of nitrogen.	Average amount of fat oxidised daily.
1-3	1.67 grammes	10.3 grammes
4-5	1.46 "	10.3 "
6-8	3.21 "	2.4 "

We see therefore that during starvation, apart from the first day or two, the animal derives the main portion of its necessary energy from the com-

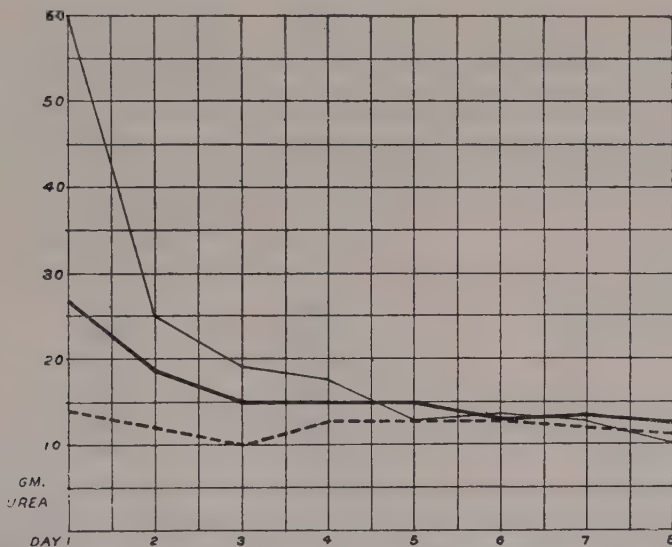


FIG. 284. Three Experiments on the Output of Urea during Starvation (dog). (TIGERSTEDT, after VORR.)

In (1) (thin line), the dog received 2500 grammes meat per day before the experiment; in (2) (thick line), the diet was 1500 grammes meat; and in the third experiment (dotted line), the meat was reduced to a minimum.

bustion of fats, provided that there is a sufficient store of these substances in the body. A certain consumption of protein is unavoidable. Since protein comes from the working tissues of the body these are spared so far as possible, and it is only when the stored fat is used up that any large call is made on the tissue protein.

BASAL METABOLISM

During starvation the energy output of the body is determined (a) by the amount necessary to keep the body alive—i.e. to maintain its warmth and to furnish the energy for respiratory movements, contractions of the heart, etc.; (b) the energy necessary to carry out any external work that is performed.

The energy requirements under (a) represent the 'Basal Metabolism' of the body. We have already seen that this varies with the weight of the individual; but if a number of different animals are compared, their meta-

bolism per kilo. is found to be greater the smaller the animal, as shown in the following Table :

	Body weight, kilos.	Calories per kilo. body weight per day.
Man	70.6	32.9
Dog 1. . . .	30.4	35.3
Dog 2. . . .	17.7	45.0
Dog 3. . . .	3.1	85.3
Rabbit 1 . . .	2.9	50.2
Rabbit 2 . . .	2.05	58.5
Guinea pig . .	0.672	223.1

This is due to the fact that the chief expenditure of energy is devoted to maintaining the temperature of the body, and the smaller the animal the larger is its surface and therewith its heat loss relatively to its weight. The basal metabolism, therefore, is more nearly a function of the surface of the body. A comparison of the metabolism per square metre body surface in different animals shows that it is practically the same in all cases, as is seen in the following Table. We may say that a warm-blooded animal requires a

	Body weight.	Calories per square metre body surface per day.
Animal 1 . . .	30.40	977
" 2	23.70	1069
" 3	19.20	1135
" 4	17.70	1040
" 5	10.90	1109
" 6	6.45	1054
" 7	3.10	1091

daily expenditure of about 1000 Calories per square metre body surface, in order to maintain its temperature and carry out such motor processes as are essential to life.

The same thing applies to man. If we desire to predict the normal basal metabolism of any given individual we must find out his surface. If we know the height and weight, the surface can be calculated by the following formula (Du Bois) :

$$S = .007184 \times W^{0.425} \times H^{0.725}$$

where S is the surface in square metres, W the weight in kilogrammes, H the height in centimetres ; or, more conveniently, by the use of a nomogram such as is shown in Fig. 285.

In adult men the basal metabolism according to Du Bois is about 40 Calories per square metre per hour. It is about 2.5 Calories less for women, and is about 1 Calorie less for each additional ten years of age from thirty to seventy years, in both sexes. Thus for a man of forty we can take 39 Calories.

It is usual to determine basal metabolism directly by estimating the oxygen usage of the resting, fasting individual, and calculating from the calorific value of oxygen at the observed respiratory quotient. The observed value can then be compared with the value predicted from the body surface. The basal metabolism, however, depends on the state of nutrition of the animal. Thus in fattening an animal, the basal metabolism increases steadily as the

animal gets fatter. It requires much more food to keep a fat animal fat, than to maintain it before fattening in its original condition. The figure 40 Calories per square metre per body surface applies to a well-nourished individual. If the food normally supplied to the individual be diminished, he can go on working as before, obtaining his energy at the expense of the fat and muscular tissues of his own body. But when under this regime the weight has fallen about 12 per cent. it is found that the basal metabolism—*i.e.* the requirements of the individual merely to keep himself alive—is also largely reduced. Thus

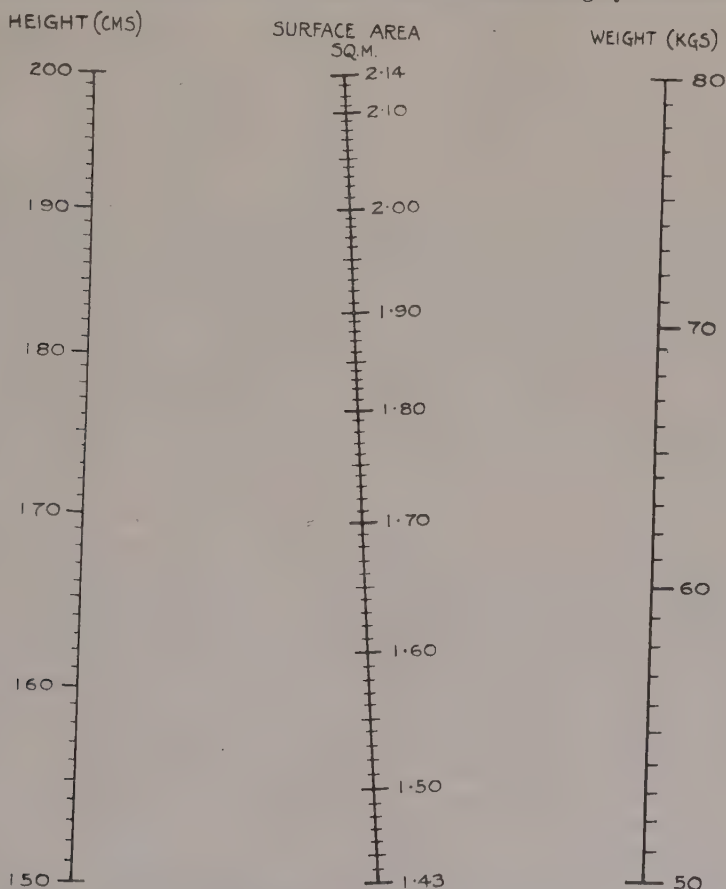


FIG. 285. Nomogram for Calculation of Body Surface. A thread or ruler, placed so as to lie on the points for weight and height, cuts the line for surface at the correct value. (W. A. M. SMART.)

in a squad of men investigated by Benedict, the food normally taken ranged from 3200 to 3600 Calories per day. After these men had by restriction of diet suffered a loss of 12 per cent. in their body weight, they were able to maintain themselves at this reduced weight and to carry out the same work as before on a diet of 2300 Calories. With further deprivation, when the body weight has been reduced by 20 per cent., there is usually a return of the basal metabolic rate up to or even above the normal level.

THE EFFECT OF FOOD ON METABOLISM

It is convenient to consider food as having a twofold destiny, *viz.* (1) to supply the energy necessary to maintain the body alive and for the

performance of work; (2) to replace the wear and tear of the body. So far as the latter function is concerned the proteins of the food take a position apart from the other two classes—fats and carbohydrates. Every working cell of the body and every muscle fibre consist for the most part of proteins with only small amounts of fats and carbohydrates. To repair the wear and tear of the machine of the body, therefore, proteins are absolutely necessary. To supply the energy requirements of the body any or all of the three classes of foodstuffs can be utilised.

A starving man is putting out energy and is diminishing in weight as a result. In the example cited on p. 507 the man was losing about 13 grammes of nitrogen a day and was putting out about 2000 Calories. These Calories came partly from the combustion of protein and partly from the oxidation of the fat. It would manifestly be useless to try to stay the loss from the body by giving the man 13 grammes of nitrogen in the food in the form of protein, since this would give him only 320 Calories towards his basal requirements of 2000. We should find in fact that the effect of such an administration would be practically to double the output of nitrogen from the body and to increase slightly the total output of energy. In the dog, it would be possible to stop the diminution of the body weight and the waste of tissues by giving an amount of protein equal to five times the loss during starvation. In man, such an amount would be too great for his assimilating powers and it would be necessary to give, in addition to the protein, fats and carbohydrates. Since the body reacts somewhat differently to these three different classes of foodstuffs, it will be convenient to deal with them separately.

THE INFLUENCE OF PROTEINS.—The protein taken in with the food on a pure protein diet has a twofold function to perform. Activity of the living tissues is associated with inevitable loss of nitrogenous materials, such as results from glandular secretions, etc. We know also that, from every epithelial surface, dead cells are being continually cast off and that a constant disintegration of red blood corpuscles goes on; and it is conceivable that similar changes may occur in other cells, such as those of the liver and of the muscles, where direct proof of destruction of tissue during normal metabolism is more difficult to obtain. It is certain that some portion of the nitrogen excreted during complete starvation must come from this source, and that one of the functions of protein food is the replacement of tissue which has been lost in this way. When, however, we are feeding an animal on a pure protein diet, by far the larger portion of the food is utilised for meeting the energy requirements of the body. In this function protein, apart from accidents of digestibility and structural adaptation of the animal's digestive arrangements to its habits of life, presents no apparent advantages over the other two classes of foodstuffs. Its value to the animal, represented numerically by its physiological heat value as 4.1, is equivalent to the value of carbohydrate and is far inferior to the value of fat with its heat equivalent of 9.3. This may be expressed by saying that protein is *isodynamic* with an equal weight of carbohydrate. If, instead of giving to the starving animal a pure protein diet, we administer a mixed diet containing also fat or carbohydrate, or both substances, sufficient to meet the normal energy requirements of the body, we can restrict the utilisation of protein more nearly to the replacement of tissue waste in the body, and are therefore able to attain nitrogenous equilibrium with a much smaller proportion of protein than is possible when this substance furnishes the whole diet. In omnivora, such as man, it is easy to attain nitrogenous equilibrium on a mixed diet

with a smaller nitrogen turnover than is found during starvation. In the experiment given on p. 507 the average nitrogen output during starvation was about 13 grammes. In Succì, the fasting man, the nitrogen output varied from 11.19 grammes on the fifth day to 2.82 grammes on the twenty-first day.

DAILY NITROGEN EXCRETION OF SUCCI IN STARVATION

Day.	N.	Day.	N.	Day.	N.
1 . . .	17.0	8 . . .	9.74	15 . . .	5.05
2 . . .	11.2	9 . . .	10.05	16 . . .	4.32
3 . . .	10.55	10 . . .	7.12	17 . . .	5.4
4 . . .	10.8	11 . . .	6.23	18 . . .	3.6
5 . . .	11.19	12 . . .	6.84	19 . . .	5.7
6 . . .	11.01	13 . . .	5.14	20 . . .	3.3
7 . . .	8.79	14 . . .	4.66	21 . . .	2.82

Chittenden has shown that in man a perfectly normal nutrition may be maintained on a mixed diet containing only 7 grammes of nitrogen daily. If the amount of fat and carbohydrate be very largely increased, it is possible to maintain nitrogenous equilibrium on even smaller quantities of protein. These results suggest that preponderance of one foodstuff will tend to excite the cells of the body to the utilisation of this foodstuff at the expense of the other two. That such is the case is shown by a study of the effect of increasing each class of food on the metabolism of the body as a whole.

Most of the experiments on the influence of variations in the quantity of protein food have been made on carnivora, such as the dog and cat. Within very wide limits, the output of nitrogen is proportional to the intake. This is shown in the Tables by Voit given below, representing two experiments on dogs.

In Experiment I. the animal had been fed for some days before with 500 grammes of meat per diem. The fact that he was excreting nitrogen corresponding to 547 grammes shows that this amount was insufficient and that he was not yet in a condition of nitrogenous equilibrium. Each day he was using up

EXPERIMENT I.			EXPERIMENT II.		
Day.	Daily meat ration.	Flesh loss per day.	Day.	Daily meat ration.	Flesh loss per day.
1	500	547	1	1500	1500
2	1500	1222	2	1000	1153
3	1500	1310	3	1000	1086
4	1500	1390	4	1000	1088
5	1500	1410	5	1000	1080
6	1500	1440	6	1000	1027
7	1500	1450			
8	1500	1500			

47 grammes of the protein tissues of his body, in addition to the 500 grammes supplied in the food. On increasing his food threefold to 1500 grammes the nitrogenous output was also increased, but a state of nitrogenous equilibrium was not reached until the eighth day of the experiment. During the six days intervening 778 grammes of meat had been retained in the body, *i.e.* there had been a retention of protein, probably in the form of increased muscular substance. The amount is too great to be accounted for by retention of the disintegration products of the protein in the body. It must have been stored

up in the form of protein and probably, to a large extent at any rate, as actual living tissue.

In Experiment II., the diminution of the protein of the food was followed by a loss of protein from the body, the output being greater than the income. The excess, however, was rapidly diminishing and equilibrium had been practically attained on the last day of the experiment. During this time the animal had excreted 14.8 grammes of nitrogen more than it had received in its food, which would correspond to a diminution of the protein store of its body, reckoned as muscular substance, by 434 grammes. Many such experiments have been performed, and they all agree in showing that in carnivora an appreciable storage of nitrogen can take place in the body. Since no fat is laid on at the same time and the animals are in a fine healthy condition, one must conclude that the greater portion of the storage takes place by a growth of muscle substance. The degree to which the storage can take place is, however, variable and is generally smaller in dogs than in cats. However much protein is given, the limit is finally arrived at where no further laying on of protein tissues of the body is possible, and the animal then enters into a state of nitrogenous equilibrium. This equivalence of income and output signifies that the extent of the total metabolism of the body is affected by the amount of protein supplied in the food, and as a matter of fact the *total energy output* of the body rises and falls with the quantity of protein in the food. This is shown in the following Table by Pettenkofer and Voit, in which the figures have been recalculated by Pflüger.

Period.	Nitrogen in food.	Nitrogen output.	Fat gain or loss.	Total Calories.
1	0	5.61	-98	1067
2	17	20.37	-61	1106
3	34	36.69	-43	1360
4	51	51.00	-24	1552
5	61	59.74	-36	1893
6	68	69.50	+ 8	1741
7	85	85.41	+ 4	2181

We see, therefore, that carnivorous animals can satisfy their total energy requirements at the expense of protein. When the protein income is in excess of their requirements, a small amount is laid on, probably as increased muscular tissue. The most marked effect, however, is an increased metabolism, which rises in proportion to the nitrogenous income. The limit to this increase is set by the powers of the alimentary canal to digest the protein. The rise in metabolism consequent on protein food is very rapid and affects the gaseous exchanges as well as the output of nitrogen. Magnus Levy and Falk found that a large protein meal might increase the respiratory exchange 40 per cent., an increase which lasted seven hours. The nitrogenous output also rises immediately after a protein meal, so that 50 per cent. of the nitrogen of the ingesta may appear in the urine within seven hours after the meal.

The whole of these results cannot be strictly applied to man, in whom it is impossible to supply all the energy requirements of the body on a pure protein diet. Even if a man eats as much meat as he can, he will be unable to obtain sufficient energy for his daily needs. Whereas the average daily requirements of a man amount to about 3000 Calories, 1 lb. of lean meat (*i.e.* entirely devoid of fat) would yield only about 400 Calories, and even if he took 4 lb. of meat daily, an amount which is impossible for most individuals, he would be obtaining only about 1600 Calories. The cures for obesity,

in which a large protein diet plays an important part, owe their efficiency to this fact. They are in all cases practically equivalent to a state of semi-starvation. Many experiments have been made on the influence of variations in the quantity of protein in a mixed diet. Within wide limits the output of nitrogen is strictly proportional to the intake. A normal adult man seems to be unable to store up protein at all, and differs in this respect from carnivora. The only way in which protein can be laid on in the body is by furnishing a physiological stimulus to the growth of muscle, *i.e.* by constant exercise. Without this it is not possible to produce growth of the muscles of the body, however much protein we may give in the diet. The conditions, however are different when dealing with an individual in whom from some cause or other the muscular tissues have not attained their full development. Thus in growing individuals a certain amount of the protein of the food is always retained in the body and laid on as tissue protein. In convalescence after great wasting of the muscles has taken place, forced feeding with large amounts of protein has been found to give rise to a considerable retention of protein in the body. This process goes on only until the muscles have attained their normal condition of development. When the tissues have, so to speak, reached 'par,' the possibility of laying on protein tissues ceases. On the other hand, protein food has in man, as in animals, a specific stimulating effect on metabolism, so that the respiratory exchange is largely increased as a result of a heavy protein meal. This effect has been named by Rubner the '*specific dynamic effect*' of protein.

THE INFLUENCE OF FATS AND CARBOHYDRATES. If either fats or carbohydrates be given to a starving animal, a certain sparing of the fat of the body takes place, but this effect according to some observers is accompanied by a distinct increase in the metabolic exchanges of the body. As regards the protein metabolism, Cathcart finds that while administration of fat increases the nitrogen output during starvation, carbohydrate food causes a diminution in the nitrogen output, and thus exercises a marked sparing effect on the proteins of the body. Voit found that during starvation, or with an insufficient protein diet, addition of fat to the food increased the total metabolism. When sufficient protein was being supplied, the addition of fat caused no increase in the total metabolism, the whole of the fat in the food being laid on as fat in the body. The stimulating effect of fat on metabolism is but slight. Magnus Levy found that the increase in the metabolism on the administration of fat to a starving animal was minimal and never exceeded 10 per cent.

Carbohydrates have a somewhat greater influence on metabolism. This stimulating influence on metabolism, although much less than that observed on the administration of large doses of protein, is easily demonstrable after administration of moderate amounts of soluble carbohydrate to a fasting subject. If carbohydrate be given in excess of the daily energy requirements, the greater proportion of it remains in the body, being stored up provisionally as glycogen, but eventually in the form of fat.

THE EFFECT OF MUSCULAR WORK ON METABOLISM

When an animal performs muscular work, the energy for the work is derived from the oxidation, directly of tissue components, but ultimately of the foodstuffs. This increased oxidation must result in increased intake of oxygen and output of CO_2 . It is a matter of common experience that any muscular exertion is attended with deeper and more rapid breathing which,

if the exertion is severe, may attain to a condition of dyspnoea. In order to determine the quantitative relationship between the increased oxidative processes of the body and the actual work accomplished, we must investigate the respiratory exchanges of an individual by one of the methods described on p. 497, in the first place during complete rest, in the second place while he is doing a measured piece of work. The following Table (Cathcart and Benedict) represents the respiratory exchanges in a trained muscular subject during complete rest and while doing moderate or severe work, viz. riding a stationary bicycle with an adjustable brake. Each observation lasted from ten to fifteen minutes.

Condition.	c.c. CO ₂ eliminated per minute.	c.c. Oxygen absorbed per minute.	Respiratory quotient.	Pulse rate.	Respiration Rate.
Lying	200	243	0.83	56	20
Moderate work	1720	1834	0.94	150	32
Severe work	2227	3265	0.98	166	38

The 'severe work' in this Table was carried to exhaustion, so that the respiratory exchanges represent the maximal augmentation of which the individual was capable for that type of exercise. This augmentation may amount to between ten and fourteen times the normal resting exchange. Similar results are obtained in observations extending over longer periods of time. Thus in one experiment the average output of CO₂ during a six hours' period of rest and starvation was 189.6 grammes. During a rest experiment with food the average output for the same period was 230.4 grammes. During work the average output of carbon dioxide in the same individual during six hours rose to 705 grammes on a carbohydrate diet, and to 634.8 grammes on a diet containing a large amount of fat. The oxidation of carbon was therefore increased more than threefold as a result of muscular work.

We can find out the relation between the actual work done and the energy expended on doing the work, either directly by allowing the work to be done in a calorimeter and measuring the total output of heat by the individual at rest and during work, or by indirect calorimetry, *i.e.* calculating from the calorific value of the oxygen consumed during the period, as determined in a respiratory exchange experiment, the amount of heat which must be set free by the oxidations involved in the performance of an accurately

ENERGY PER DAY.

Nature of experiment.	Heat eliminated.			External work in Calories.	Total in Calories.
	By radiation and conduction.	In urine and faeces.	In water vaporised from lungs and skin.		
Rest with food (average of four days)	1850	26	521	—	2397
Rest, fasting (four experiments) (average of five days)	1605	21	561	—	2187
Work (fourteen experiments) (average of forty-six days)	3802	29	743	546	5120

measured amount of work. For conversion of the work done into Calories, we know that $1 \text{ Kg} - \text{M.} = \cdot 0024 \text{ Calorie}$, or $1 \text{ Calorie} = 426 \text{ Kg} - \text{M.}$ In the Table on p. 516 are given the results of an experiment by Atwater by the direct method. The work done by the man on a bicycle ergometer with a brake was also accurately determined, and is given in the Table in terms of its heat equivalent, viz. as Calories.

In the above experiments, the mean expenditure of energy on the work days was 5120, and on the rest days (with food) 2397 Calories, a difference of 2723 Calories. This represents the excess metabolism over resting requirements, which must take place in order that the body may perform work equal

to 546 Calories. The fraction $\frac{\text{work}}{\text{total energy evolved} - \text{resting metabolism}}$

is spoken of as the 'mechanical efficiency' of the body. In the above case it equals one-fifth, and the body is said to have a 20 per cent. efficiency. Of course a certain proportion of this excess of energy used over work done is accounted for by the increase in the work which must be performed by the respiratory muscles and heart. Even if we neglect these factors altogether, the efficiency of the body as a machine corresponds to between 16 and 25 per cent., an efficiency which exceeds that of the best of our steam engines and is only equalled by certain internal combustion engines. In some cases the mechanical efficiency may attain as much as 30 per cent.

Can we employ these results to throw light on the nature of the constituents of the body which undergo oxidation to furnish the energy of muscular work? In the experiment already quoted, the oxidation of carbon was increased more than threefold during a six-hour period of work. This carbon might form part of the molecule of protein, fat or carbohydrate; but if we compare the protein metabolism of the same individual during these experiments no corresponding alteration is observed. During rest and starvation the average output of nitrogen per day corresponded to the destruction of 82 grammes of protein. During rest and with an approximately sufficient amount of food, the average daily consumption of protein was 98.8 grammes. During a work day, in which the individual received the same amount of protein in the food and a somewhat insufficient quantity of carbohydrates and fats, the consumption of protein was 109.4 grammes. Thus there was a three- to fourfold increase of the carbon metabolism of the body, but only a 10 per cent. increase in the protein metabolism.

The study of the respiratory quotient also gives us some idea of the nature of the material which is furnishing by its oxidation the necessary energy for the performance of muscular work. If the whole of the animal's energy requirements were furnished by the oxidation of carbohydrates, the output of carbon dioxide expired would be exactly equal in volume to the

oxygen taken in, and the *respiratory quotient* of the animal, namely $\frac{\text{CO}_2 \text{ expired}}{\text{O}_2 \text{ inspired}}$,

would be equal to unity. Thus: $\text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 = 6\text{H}_2\text{O} + 6\text{CO}_2$. If we compare the formulæ of a carbohydrate and a fat respectively, it is evident that it will require a relatively larger amount of oxygen to oxidise the fat than is necessary in the case of the carbohydrate. When fats undergo oxidation, of the oxygen used only a portion is devoted to the formation of carbon dioxide, the rest being employed in the oxidation of hydrogen to water. In an animal using only fats, the carbon dioxide output of the body would be considerably less than the oxygen intake and its respiratory

quotient would be less than unity. The respiratory quotients for protein, fats and carbohydrates are given in the following Table.

Material.	Respiratory quotient $\frac{\text{CO}_2}{\text{O}_2}$ (volumes).
Carbohydrate	1.0
Protein	0.81
Animal fat	0.707

Since the carbon dioxide excreted during exercise may result from the oxidation of protein, fat or carbohydrate, we cannot deduce directly the total energy set free in the body by an estimation of the CO_2 output alone. The respiratory quotient must also be determined, in order to throw light on the real amounts of fat and carbohydrate consumed, and in accurate experiments the output of nitrogen in the urine must also be measured. Every gramme of nitrogen in the urine, if resulting from the oxidation of protein, corresponds to the intake of 8.4 grammes (5.88 L.) oxygen and to the output of 9.35 grammes (4.76 L.) carbon dioxide. If the amounts of CO_2 and oxygen corresponding to the protein metabolism be deducted from the total respiratory exchanges, the remainder must be due to the metabolism of fat and carbohydrate, and the respiratory quotient obtained after deducting the gaseous exchanges due to protein metabolism will give the proportions of fat and carbohydrate oxidised. The following Table gives the relative combustion of carbohydrate and fat for a given respiratory quotient :

R.Q.	Carbohydrate.	Fat.	Calories for one litre oxygen.
1.00	100 per cent.	0 per cent.	5.047
0.95	83 "	17 "	4.985
0.90	66 "	34 "	4.924
0.85	49 "	51 "	4.863
0.80	32 "	68 "	4.801
0.75	15 "	85 "	4.739
0.707	0 "	100 "	4.686

The number of Calories set free in the body for every litre of oxygen taken in are also given in the above Table.

The respiratory quotient in an animal is therefore a net result determined by the average nature of the substances which are undergoing oxidation in its body. If the performance of muscular work involved special chemical processes, *e.g.* a metabolism of one of the main constituents of the body in preference to either of the others, this sudden change in the quality of the metabolism should show itself in the respiratory quotient.

According to Speck and Loewi, moderate muscular work which is not associated with dyspnoea, although attended by a large increase in the CO_2 output and oxygen intake of the body, does not alter the respiratory quotient. In such experiments the respiratory exchanges are taken over a considerable length of time. It is a familiar experience that a man can carry out severe muscular work on very various diets, according to the habits of his class and race. The respiratory quotient over a long period, such as a day, must depend on the food which is consumed, irrespective of the amount of muscular work which is done in the time. Ultimately there is no doubt that the energy for muscular exercise can be derived from any of the three classes of food, carbohydrates, fats and proteins. Such experiments, however, do not answer the question as to the immediate origin of the energy involved in muscular contraction. We shall see later on that the body has the power of converting carbohydrates into fats, and proteins and fats into carbohydrates. The respiratory quotient in the course of a day is affected by these intermediate changes, as well as by the oxidised foodstuffs. Dealing with

frog's muscle we saw that the sole source of the energy of contraction was the glycogen of the muscle. The respiratory quotient of the gaseous exchange in an *isolated* contracting muscle is therefore equal to unity. The most careful experiments have failed to show any consumption of the fat or nitrogenous constituents of the muscle in this process, and any such change would give rise to a respiratory quotient less than unity. In the Table given on p. 516, the muscular exercise carried on over a period of fifteen minutes is seen to cause a rise of the respiratory quotient, suggesting that carbohydrates represent the immediate, or at any rate the most readily available, source of muscular energy. Various precautions have to be taken in carrying out the determination of the respiratory quotient under these conditions. Muscular exercise is attended with an initial quickening of respiration which is to some extent voluntary. This quickening and deepening may be in excess of the respiratory needs of the moment, and will give rise to a washing out of the carbonic acid of the blood and an increased respiratory quotient. In violent exercise, lactic acid not only accumulates in the muscles but passes into the blood, there setting free a certain amount of carbonic acid and raising the tension of this gas in the blood. The excess of carbonic acid augments the pulmonary ventilation, quickens and deepens the respiratory movements and increases the CO_2 output by the lungs. We may therefore at the beginning of violent exercise have a respiratory quotient well over 1.5. When exercise has ceased, the acid in the blood is gradually oxidised, or perhaps passes back into the muscles. As it disappears from the blood, some of the CO_2 produced by its oxidation is retained so as to preserve the reaction of the blood as nearly normal as possible. During this period, therefore, there may be a fictitious diminution of CO_2 output and a lowering of the respiratory quotient. To determine, therefore, the true gaseous exchanges associated with a given amount of muscular work, we must first take the resting metabolism. We may suppose that the subject of the experiment is taking in 350 c.c. of oxygen per minute and expiring 300 c.c. of CO_2 . He then takes fairly violent exercise (the most convenient being stepping at about 150 times per minute) for one minute. He then rests for twenty minutes. During the whole time he is expiring into a series of Douglas bags. At the end of twenty minutes it is found, if the exercise has not been too severe, that the respiratory exchange has returned to what it was before the experiment; the excess of the oxygen inspired for the twenty minutes, and the excess of CO_2 expired over those amounts which would have been inspired and expired if the subject had continued at rest in a chair, is taken as the 'excess' metabolism associated with the muscular exercise.

Experiments by A. V. Hill and Furusawa have shown that, measured in this way, the oxygen intake associated with muscular exercise is equal to the CO_2 output, *i.e.* that the respiratory quotient is unity. The conclusion is clear, therefore, that in man, as in the isolated frog's muscle, the sole *immediate* source of the energy of muscular exercise is the carbohydrates of muscle. Other substances in the body, such as proteins and fats, can serve as a source of energy, but only after conversion into carbohydrate. On this account we find that after long-continued severe exercise, the period of increased metabolism is followed by a period during which the respiratory quotient sinks to a very low level, which is interpreted by Hill and others as showing that fats during this time are being converted into carbohydrates to replace the exhausted stores in the liver and muscles. Even on a pure fat diet there is no evidence that muscles can utilise this class of substance immediately. After two or three days on a pure fat diet, a short bout of exercise lasting one minute gives the same respiratory quotient of unity as in a man fed normally. Under

these conditions, however, fatigue rapidly supervenes, and in prolonged experiments, as shown in Figure 85, p. 182, the gaseous exchanges as a result of exercise may give a quotient appreciably below unity.

As the result of another series of experiments Krogh has come to the conclusion that the cost of work in man, when it is performed at the ultimate expense of fat, is 10 per cent. more than when it is performed at the expense of the carbohydrate of the body. This extra expenditure of energy Krogh regards as, so to speak, wasted in the chemical conversion of fats into carbohydrates. This great difference does not arise in the case of proteins, which form carbohydrates in the body with extreme ease. But whereas proteins form, for the most part, the working tissues of the body, fats are stored as a reserve food, so that under normal conditions, in default of an excessive diet of proteins, fats must often be utilised for the carrying out of muscular work. For this to take place, it is essential that they be first converted into carbohydrates and stored in the muscles as glycogen.

It will be noticed that, in contradiction to popular opinion, the proteins do not play any special part in relation to muscular exercise. The special value of protein is for building up the body and for repairing wear and tear. As a source of energy it presents no advantages over carbohydrate and fat; in fact it may be in some respects inferior to these substances or at any rate less economical, owing to the fact that ingestion of protein causes an increased metabolism, the whole of which appears in the form of heat. If an animal after a protein meal be made to work, the increased metabolism due to the specific dynamic action of the protein is still observed over and above that due to the performance of work. The output of energy of a man on a large meat diet doing a certain amount of work will therefore be greater than if the same amount of work were performed on a diet consisting largely of carbohydrates and fats. On the other hand, in training we have to consider not only the performance of work done during the training, but also the necessity for building up the muscular tissues of the body. Under these conditions there is some reason for a plentiful supply of protein in the diet. When, however, a man has to undertake a certain amount of muscular exercise every day and has arrived at the full development of his muscular system, there is no need to attempt to supply the energy for his movements at the expense of foods rich in protein, such as meat. In many cases the beneficial effects of so-called meat are due to its content in fat—this foodstuff presenting advantages over carbohydrates when large quantities have to be ingested to supply the daily energy requirements of the body.

THE SIGNIFICANCE OF THE FOODSTUFFS

In order to keep an animal alive, a certain amount of food must be supplied to replace the loss to the body of its tissues and of its reserves of carbohydrates and fat, which are being continually consumed for the provision of the energy necessary to keep the animal warm and for the performance of the internal and external movements of the body. The actual amount of food required will depend on the size of the animal, on the temperature of the surrounding medium and on the muscular work performed. For supplying this energy any of the three classes of foodstuffs may be utilised, the value of each being given by the Calories evolved when the foodstuff is oxidised to the end stages which it attains in the body. Thus carbohydrates and proteins are *isodynamic*—i.e. give rise to the same amount of energy in the body for a unit weight—1 gramme of each giving out 4.1 Calories. Weight for weight, fat has double the value of either of these two classes, its Calorie value being 9.3. This isodynamic equivalence of the foodstuffs is, however, interfered with to a certain extent by the specific dynamic action already spoken of, in virtue of which protein has an excitant action on the processes of oxidation occurring in the body, so that an animal fed on a largely protein diet will give out more heat and consume more food than if it were fed on a diet of the same Calorie value but in which carbo-

hydrates preponderated. This specific dynamic action is not altogether lacking in carbohydrates and fats. Thus, according to Rubner's experiments, for every 100 Calories of protein ingested there is an increased heat production over the fasting level of 30 to 35 Calories, while fat gives an increased heat production of about 12 per cent., and sugar of about 5 per cent. On account of this specific dynamic action, an average mixed diet, in order to maintain the body in a state of equilibrium, must have a Calorie value of 13 to 14 per cent. higher than the sum total of the Calories given off during fasting. Thus, supposing a man while fasting and in bed gives off 1800 Calories a day, which would be derived from using up the tissues of his body, he would under the same circumstances give off about 2000 Calories if he received a minimum mixed diet just sufficient to maintain his body weight constant. This specific dynamic action of protein might be regarded as mere waste or '*luxus consumption*,' since it results only in the production of heat and cannot be utilised for the performance of muscular work. It must be remembered, however, that in cold surroundings a large proportion of the food must always be applied to maintain the body temperature, and for this purpose the excess heat involved in the consumption of protein, and to a less extent of other foods, can be, and is, utilised. Hence it comes about that in order to exhibit this specific dynamic action, the animal must be kept at a temperature of about 33° Centigrade. Below this temperature the specific dynamic action of the foodstuffs becomes less and less apparent, and is finally merged in the heat production necessary, whether food is taken or not, to keep up the temperature of the body.

Even regarded simply as a source of energy, proteins are distinguished from carbohydrates and fats by the fact that no means are provided for the storage of proteins in the body, except by the growth of muscular and other tissues. This growth is normal in the young animal, and in the adult in convalescence from wasting diseases and during recovery from a period of insufficient feeding. There is a certain maximum of growth beyond which the living tissues of the body cannot attain. Arrived at this stage, the body cannot add to its protein store, and therefore all the protein that is ingested and absorbed from the alimentary canal is at once broken down and burnt up in the body. If we examine the curve of nitrogenous excretion in the urine, we find that practically all the nitrogen taken in as protein in the food is turned out within twelve to sixteen hours. Thus, if a man is on a mixed diet sufficient for his daily needs, a doubling of the protein in the diet, leaving the other constituents unchanged, will result in a doubling of the nitrogenous excretion and a storing of the fats and carbohydrates that would otherwise have been consumed, so that these will be laid on as fat in the body. On the other hand, an increase of the fats or carbohydrates will not increase the carbon metabolism of the body, but any excess above the daily needs, if absorbed, is stored up in the body in the form of fat. To increase the protein metabolism therefore, all that is necessary is to increase the protein in the body; to increase the carbohydrate and fat metabolism it is necessary to increase the metabolism as a whole, either by muscular exercise or by exposure to cold.

Protein is also distinct from fats and carbohydrates in that it is essential for the repair of the wear and tear of the tissues. We may thus speak of the protein of the food as having a twofold destiny. A certain proportion is used to repair tissue waste; the amino-acids into which it is resolved in the intestines circulate in the blood, and each living cell picks out those amino-acids which are essential for building up the protoplasm of the cell. Protein with this destiny exerts no specific dynamic action, and this action

is therefore inconspicuous in the infant, which is storing up in new tissue a part of the protein which it takes up in its food. The rest of the protein, after resolution into amino-acids, loses its nitrogen which appears in the urine chiefly in the form of urea, and the remaining part of the protein molecule then undergoes rapid oxidation. The nitrogen of the urine is therefore derived, partly direct from the nitrogen rapidly split off from the protein of the food, partly from the disintegrated proteins which have formed part of the living fabric of the cells.

Folin has brought forward a number of facts, which point not only to a twofold origin of the nitrogen of the urine, but also to a qualitative difference in the two orders of protein metabolism. Whereas in the urine of man on a normal diet the urea nitrogen forms 85 per cent. or more of the total nitrogen, a reduction of the protein ration to the minimum necessary to meet the nutritional requirements of the body causes, not only an absolute diminution of the urea but a large relative diminution when compared with the other constituents of the urine, such as creatinin. He concludes therefore that the nitrogenous end products of nutritional metabolism are different from those of the energy metabolism. There is also a difference in the time relations of the two orders of metabolism. Whereas the nitrogen is rapidly eliminated when protein is being utilised for the supply of energy to the body, the occurrence of increased tissue waste causes a rise of nitrogenous excretion, which comes on slowly, often after the lapse of a day, and may last two or three days. The process of protoplasmic disintegration appears, therefore, to occur in a series of stages, which occupy a considerable time and end in the production of substances qualitatively distinct from that substance, urea, which is the almost exclusive nitrogenous end product of the energy metabolism of protein.

ACTION OF THE PRODUCTS OF PROTEIN DIGESTION

Proteoses, Peptones and Amino-acids. In the digestion of the naturally occurring proteins, the first products of hydration consist of a mixture of substances known as proteoses and peptones. In the further processes of digestion these substances are converted into the amino-acids which form the proximate constituents of the protein molecule. In nearly all cases it has been found that the meat in the diet of an animal can be replaced by a corresponding quantity of the products of pancreatic digestion of the same meat, without interfering with the nitrogenous equilibrium of the animal, and it has also been shown that the same result may be attained by slowly injecting into the circulating blood the products of pancreatic digestion of protein, *i.e.* a mixture consisting almost entirely of amino-acids. Since the proteins of the body differ in their composition from the majority of the proteins of the food, it is evident that each hydrolysis molecule has to be entirely disintegrated and reconstructed before it can take its place in the body fabric; and it is therefore only natural that, so far as metabolism is concerned, the results should be identical whether we feed the animal with the ordinary food-protein or with the products of its hydrolysis. This latter mode of feeding cannot, however, be regarded as presenting any advantages. Under normal circumstances the products of hydrolysis are set free in small quantities at a time and can therefore be absorbed and disposed of in proportion as they are set free. On the other hand, a sudden flooding of the alimentary canal with a large quantity of the products of digestion introduces an abnormal factor, which must tend to produce wastage of nitrogen in the body.

THE BIOLOGICAL VALUE OF DIFFERENT FORMS OF PROTEIN

In consequence of the wide variation in the composition of the proteins contained in the different tissues of the body, it is necessary that the food shall include all the amino-acids in proper quantities and proportions. Hence it follows that all proteins are not equivalent as regards their capacity for replacing tissue waste or serving for the growth of the animal body. Those in which nearly all the amino-acids are represented and which contain these in proportions approximating the average of those found in the chief animal proteins will be more valuable than those (1) in which one or more of the chief amino-acids are absent, or (2) in which there is a large preponderance of one or more of the amino-acids which are required only in small proportions for building up the tissues of the animal body. As an example of the first type we may instance collagen and gelatin, and zein, the chief protein of maize. Collagen and gelatin on digestion yield the ordinary amino-acids of the fatty series and also a certain amount of phenyl alanine and proline. The oxyphenyl group which occurs in other food proteins in the form of tyrosine, as well as the indol-containing group tryptophane, are absent, so that gelatin if pure gives neither Millon's test nor the glyoxylic test. Hence gelatin cannot entirely replace the proteins of the food. Its capacity for yielding energy to the body equals that of any other protein, but it can only replace body protein when the missing amino-acids are also supplied. Physiologists have indeed succeeded in maintaining animals for a short time in a state of nitrogenous equilibrium on a diet containing as its sole nitrogenous constituent a mixture of gelatin with tyrosine and tryptophane. In the same way zein, yielding no tryptophane, is incapable by itself of supporting life, though this can be accomplished if lysine, tyrosine and tryptophane are administered at the same time.

As an example of the second type we may instance the protein of wheat flour. Whereas caseinogen, the protein of milk, contains only 15 per cent. of glutamic acid and serum albumin only 7 per cent., gliadin, the chief protein of flour, contains as much as 36 per cent. If wheat flour is the main or sole source of protein to the body, it is evident that a large amount of glutamic acid will be in excess of that required to replace tissue waste. These differences in chemical composition between the proteins are of significance when the protein of the food is reduced to the minimal amount required to replace tissue waste, and under such circumstances marked differences are observed between the biological values of proteins.

Thomas attempted to give a numerical value to the biological value of proteins in the following way. On a diet containing large quantities of starch and sugar and only a trace of protein, he found the minimal loss of body protein. He then investigated how much of each of the various proteins must be added to the diet in order to prevent any loss of tissue protein. The biological value of the protein could then be found by the following formula :

$$BV = 100 \frac{\text{Urine N in N-free diet} + \text{faeces N} + \text{balance}}{\text{N-intake}}$$

In this way he calculated the biological value of a number of different proteins. It has been pointed out, however, by C. J. Martin and Robison that Thomas' experiments were too short to give reliable results. Most of them did not last more than three or four days, in which time no sort of nitrogenous equilibrium is arrived at. Reference to the graph in Fig. 286 shows that when a nitrogenous diet is suddenly replaced by a diet consisting only of carbohydrates and fats, there is a lag of four or five days before the nitrogen falls to its starvation value; and when the nitrogen intake is once more restored to its previous amount, the same length of time is necessary for the attainment

of nitrogen equilibrium. Experiments to determine the nitrogenous value of protein are therefore very laborious. Martin and Robison confined their attention to only three kinds. The principles involved in this determination are embodied in the diagram (Fig. 287). In this diagram $OM = m$ is the nitrogenous output on a N-free diet of

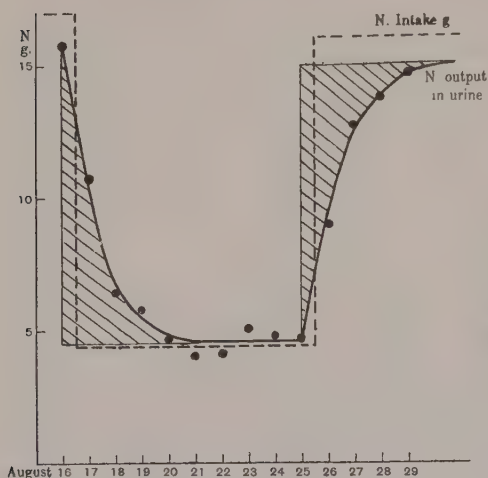


FIG. 286.

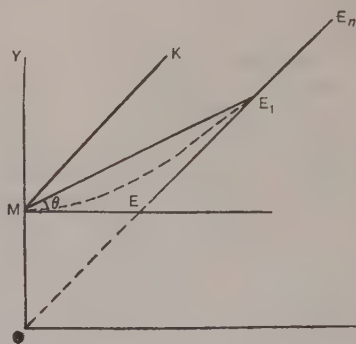


FIG. 287.

adequate fuel value, so m represents the nitrogen minimum. If an ideal protein ($BV = 100$) could be found and fed in gradually increasing amounts, the N output will remain constant so long as the intake is less than m . The food protein will simply save an equal amount of body protein. The graph of intake and output will therefore be parallel

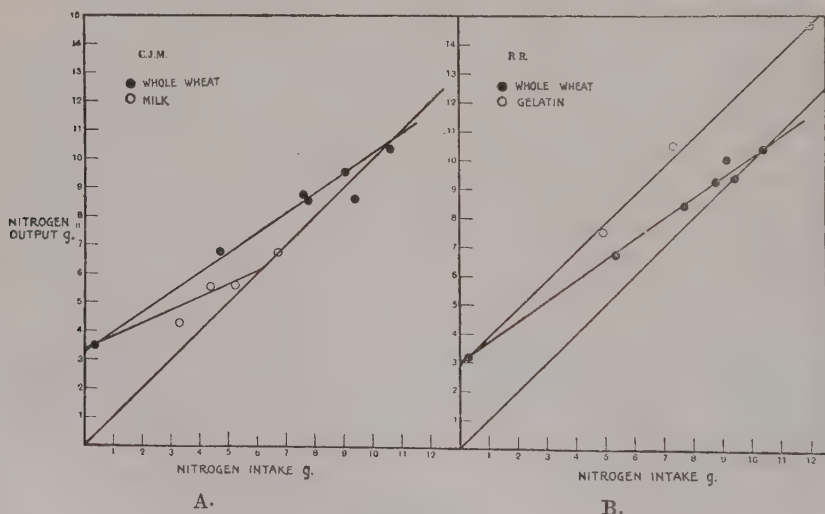


FIG. 288.

to X axis, and at E , where $ME = MO$, the body will be in nitrogenous equilibrium. If now the intake be further increased, the graph will follow the line EE_n at an angle of 45 degrees to the axis. In the case of a protein of less value than the ideal protein, equilibrium will not be attained on an intake $= m$, but on some greater amount e_1 (at the point E_1). On all amounts less than this, the output will exceed the intake, and the graph will follow some line joining ME_1 . We can express the biological value of such a protein in the following way. If y is the N output corresponding to any N intake

x less than e_1 and θ is the angle made by the line ME_1 to the abscissa, 'Thomas' formula becomes

$$\begin{aligned} BV &= 100 \frac{m + (x - y)}{x} \\ &= 100 \frac{m + x - (x \tan \theta)}{x} \\ &= 100 (1 - \tan \theta). \end{aligned}$$

If the protein were unable to satisfy any portion of the body's requirements, its graph would be a straight line, MK parallel to OE, since the nitrogen output would be always equal to the intake + m . For this line $\theta = 45$ degrees, while the biological value $100 (1 - \tan 45 \text{ degrees}) = 0$.

The diagrams in Fig. 288, A and B, show the biological values of whole wheat protein, of whole milk protein and of gelatin, determined by Martin and Robison on these principles. The whole wheat gave a biological value of thirty-five for one individual and thirty-one for another individual. The milk protein gave a biological value = 51. The line for gelatin, on the other hand, ran parallel to the equilibrium line which it never cut, so that its biological value must be regarded as *nil*.

The practical outcome of Thomas' experiment is that when there is scarcity of protein, animal protein is more economical than vegetable protein; and that if it is necessary to live on a purely vegetable diet this should be mixed, so that all the amino-acids required in the body may be represented in the diet.

THE INORGANIC FOODSTUFFS

If an animal be fed with the proper quantities of fats, proteins and carbohydrates, from which all the salts have been removed, it rapidly shows a distaste for the food, becomes ill, and dies in a shorter time than if it were receiving no food at all. Part of the symptoms which occur in these cases are due to the production of acid substances, *e.g.* sulphuric acid, in the course of metabolism of the proteins. It is possible to obviate this acid intoxication by administering sodium carbonate with the food. This admixture, however, suffices to prolong the life of the animal only for a short time. It is evident therefore that the inorganic constituents of the food are as essential for the maintenance of life as the energy-yielding foodstuffs, namely, proteins, carbohydrates and fats. In the course of this work we shall have occasion to study the intimate dependence of the functions of various tissues, such as skeletal and heart muscle, on the presence of salts in normal proportions in the fluids with which they are bathed. Animals in a state of salt hunger show that the presence of salts is equally requisite for the due performance of the processes of secretion and absorption. Towards the end of the experiment the animal vomits its food, which presents no signs of digestion, even when it has lain some hours in the stomach. Forster has shown that in salt-hunger the body is continually giving off inorganic constituents in the urine. The amount of these is smallest when it is supplied richly with organic foodstuffs. It seems that certain inorganic ions are held in a state of combination with the tissue constituents, especially the proteins. If the amount of food supplied is insufficient, the animal lives on its own tissues, thus setting free salts which appear in the urine. An interesting condition is miner's cramp, met with in workers who drink water and perspire freely in hot mines. So much sodium chloride is lost in the sweat that, as J. S. Haldane showed, the urine, though small in bulk, is sometimes quite free from chloride. The cramp is due to excess of water in the tissues, and can be avoided by the subject drinking water containing 10 grains of salt per gallon (0.015 per cent.).

THE WATER BALANCE. Some 70 per cent. of the body consists of water, and the water content of the tissues is maintained reasonably constant by equalisation of the loss and gain of water.

The gain of water is derived from two sources, viz. water taken in as such with food or drink, and water formed by the oxidation of foodstuffs. The output of water is by the lungs, skin, urine and fæces.

The water formed by oxidation of foodstuffs can be calculated on the assumption that, from 100 grammes of each of the proximate principles, the following amounts of water are derived :

From protein	.	.	.	.	.	.	.	41 grammes.
„ fat	.	.	.	.	.	.	.	118 „
„ carbohydrate	.	.	.	.	.	.	.	55 „

Calculation on this basis shows that with average sedentary diets about 350 c.c. of water per day are formed by oxidation.

The total exchange of water per day is approximately as follows for average conditions for an adult :

Income.				Output.			
Drink	.	.	1,450 c.c.	Urine	.	.	1,500 c.c.
Food	.	.	800 „	Skin	.	.	600 „
Oxidation	.	.	350 „	Lungs	.	.	400 „
				Fæces	.	.	100 „
2,600 c.c.				2,600 c.c.			

With alterations of body-weight there is usually a proportional loss of water and of solid constituents, but in some cases there is a proportionally greater loss or gain of water, which it is important to take into account. A loss greater than 20 per cent. of the body water is not usually compatible with life.

ACCESSORY FOOD SUBSTANCES OR VITAMINS

If we feed an animal on a mixed diet containing proteins, fats, carbohydrates and salts in the proper proportions, but in a state of purity, *e.g.* a mixture of caseinogen, starch, sugar, salts and lard, we find that the animal becomes ill, ceases to grow if a young animal, and finally dies. This had already been pointed out in 1880 by Lunin, but the matter was taken up again by Hopkins, who worked on young growing animals. He found that in the case of rats it was sufficient to add 3 c.c. of fresh milk to the artificially compounded diet, for growth to take place normally. Three cubic centimetres of milk contain only 0.08 gramme total solids, of which the greater part consists of caseinogen, fat, salts and lactose already present in the artificial diet ; yet this small amount of fresh milk enabled the rats to add 0.5 gramme a day to their weight. These observations were the beginning of a lengthy series of experiments by many different observers. It has been found that practically all fresh foods contain small traces of substances to which the name 'vitamins' has been given. They have never been isolated and exert their effect in infinitesimal quantities. They are essential for the utilisation of the food, for the maintenance of health and for growth. Five or six such vitamins have been distinguished, not by isolation, but according to their different properties and mode of action.

They are distinguished by letters. Vitamins A, D and E are soluble in fats and occur naturally in association with them, while B and C vitamins are water-soluble. In experiments on the vitamins, animals are fed for several weeks on a diet deficient only in the vitamin concerned, and are compared with controls fed with diet containing the vitamin.

Vitamins-A and -D. These often occur together. *Vitamin-A* is essen-

tial for growth and its absence leads to failure of growth, an affection of the cornea called xerophthalmia, a general lowering of resistance to infection, and ultimately death. It is originally formed, as has been shown by Miss Coward, in the growing green plant, and it is doubtful whether any higher animals have the power of forming it in their bodies. The cow, for instance, obtains its A-vitamin from grass: after ingestion it is absorbed into the fat of the body and of the milk, so that it is taken by man largely in the form of butter or milk. It was the absence of this substance which was especially responsible for the absence of growth in Hopkins' experiments represented in Fig. 289. It is contained in large quantities in cod liver oil, and in even larger amounts in the oils from mammalian liver. Its origin in the sea is especially in the green diatoms which serve as food for the small plankton,

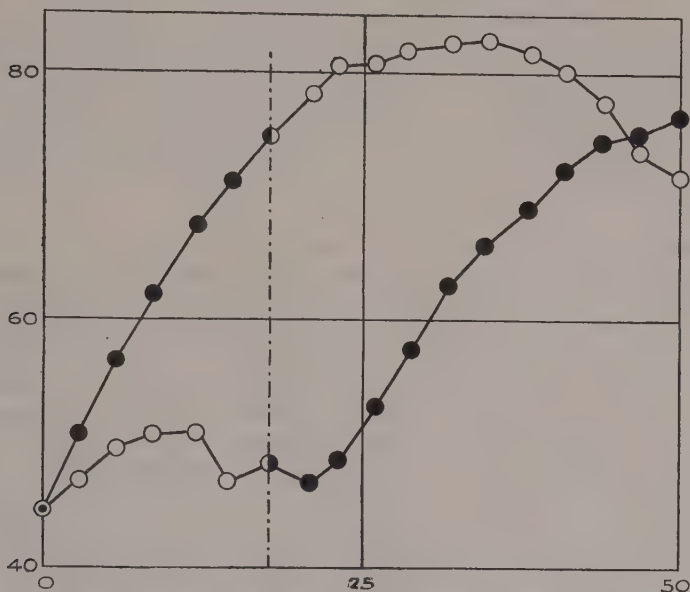


FIG. 289. Two Curves showing Growth of Rats with and without "Vitamin-A."

Lower curve (up to 18th day) eight male rats on pure dietary; upper curve eight similar rats taking 3 c.c. of milk each a day. On the 18th day, marked by vertical dotted line, the milk was transferred from one set to the other. Average weight in grammes vertical; time in days horizontal. (F. G. HOPKINS.)

organisms which are the basis of the food supply of the larger inhabitants of the sea. It is not destroyed by heat, but is easily oxidised. It is absent from most specimens of lard and from many vegetable oils, such as olive oil. If, however, pigs are fed on green food, pig fat contains the vitamin. It is much more abundant in the milk of cows in summer, out at grass, than when these animals are kept in stables and fed on oil-cake, &c. Although fat-soluble, it is not itself a fat. Drummond has shown that the fats can be removed by saponification in the absence of oxygen, leaving the vitamin intact. The residue, which contains cholesterol and vitamin, can be freed from the cholesterol and still contain the vitamin, which appears to persist in the fraction consisting of unsaturated alcohols and hydrocarbons, but in such minute quantities that any attempts to define more closely its chemical characters have failed. It can be stored in the body to a certain extent, so that the effects of its absence from the food are not perceptible till after a few weeks.

It was shown by E. Mellanby that the absence of growth in vitamin lack is associated with the abnormal growth of bones, which gives rise to the changes associated with the disease of rickets. An important factor in the causation of rickets is the absence of *Vitamin-D*, which is therefore often called the anti-rachitic vitamin.

The most marked change in rickets is a defect in the ossification normally occurring at the epiphyseal line. Ossification in cartilage consists of the following stages: (1) multiplication of cartilage cells; (2) calcification of the cartilage; (3) absorption of the calcified cartilage; (4) deposition of true bone, *i.e.* calcified fibrous tissue, round cells—osteoblasts—which have invaded the calcified cartilage from the marrow. In rickets there is an accelerated multiplication of cartilage cells and a retardation in the deposition of true bone, from a failure in the process of deposition of calcium salts. It is evident that in the causation of rickets, or for the growth of normal bone, many factors are involved. In the first place, the presence of D-vitamin is necessary. This may, however, be replaced to a certain extent by exposure to the sun's rays or to ultra-violet light. Then it is necessary that calcium salts shall be present in proper amount. Deficiency of calcium and phosphates in the diet may therefore hinder the formation of bone. It has been shown by Robison that, in the carriage of calcium salts to the bone, a part may be played by such substances as a hexose monophosphoric ester which forms soluble salts with calcium. Substances of this type have been detected in blood. Under the action of an enzyme which is present in ossifying cartilage, this calcium salt is hydrolysed, and calcium phosphate with a certain amount of calcium carbonate is precipitated in the matrix round the osteoblasts.

It is interesting that exposure of the animals to sunlight, or to ultra-violet light, can replace to a certain extent the necessity for the presence of D-vitamin in the food. Investigation of the cause of the similarity between the effect of addition of vitamin-D to the diet and exposure of the animal to ultra-violet light, led Steenbock to the remarkable discovery that vitamin-D is produced by the action of ultra-violet light on a precursor, apparently a sterol, which is present in the tissues, including the skin. It was further found by Rosenheim and Webster that this precursor, frequently found in association with cholesterol, is another sterol called *ergosterol*, $C_{27}H_{42}O$. Ergosterol has a characteristic absorption spectrum in the ultra-violet region. Irradiated ergosterol has all the properties of vitamin-D, and is intensely powerful in its effects, $\frac{1}{100,000}$ mg. sufficing to produce an anti-rachitic effect in a rat. Vitamin-D also produces growth effects to a minor extent, but its chief effect seems to be in controlling the balance of calcium and phosphorus.

Vitamin-B. In races whose staple diet consists of rice, prolonged feeding with polished rice, *i.e.* rice from which the husks have been removed, leads to the production of the disease known as beri-beri. This is distinguished by the occurrence of pains and weakness in the limbs, loss of sensation in the skin, cedema, and weakness of the heart. A somewhat similar disease may be produced by the same means in fowls or pigeons. The disease may be cured by adding the polishings, *i.e.* the part of the rice grain which has been removed, to the polished rice before eating. It is evident that some substance is removed during polishing, which is essential to the normal nutrition of the body. The substance occurs in the rice embryo and also in that of wheat, in yeast, in eggs, and in smaller quantities in various vegetables and milk. It is spoken of as B- or water-soluble vitamin. It is not stored to any extent in the body, so that animals show the effects of its withdrawal more rapidly than they do the effect of withdrawal of the A-vitamin. Absence of B-vitamin leads in rats to wasting, failure of growth, atrophy of the testes and sterility.

The wasting is due to lack of appetite and digestive disturbances. It is now recognised that at least two substances are responsible for the properties of vitamin-B. Provisionally these have been called B_1 and B_2 ; they can be differentiated by their physiological action and by the action of heat and

alkali, either or both of which destroy B_1 . Though both are necessary for growth, the B_1 vitamin is believed to be related to beri-beri, while B_2 has been correlated with the nutritive disorder in man known as pellagra. Yeast is rich in both, wheat germ in B_1 , and milk, meat and green vegetables in B_2 .

Vitamin-C. This may also be called the antiscorbutic vitamin. Scurvy is a deficiency disorder which has been long known: it occurs when men are cut off for a long time from fresh food, especially vegetables. Its main symptoms are weakness, skin eruptions, small hæmorrhages under the skin, and hæmorrhage from the gums and other mucous membranes. It is prevented or cured by the administration of fresh food, especially fresh vegetables, or of fruit juice, oranges and lemons being specially rich in C-vitamin. In an acid medium this vitamin will stand exposure to boiling point for some time, but it is destroyed by oxidation almost at once on heating in an alkaline medium. The practice of adding alkali to preserve the colour of vegetables when they are cooked is therefore bad. This vitamin is present in small quantities in fresh meat and eggs. It is absent from most grains, but is formed when these grains germinate. When fresh vegetable food cannot be obtained, scurvy may be prevented by feeding with beans which have been moistened, and allowed to germinate in a warm place for twenty-four to forty-eight hours. For experimental work on vitamin-C, it is usual to employ guinea-pigs.

Vitamin-E. Recent experiments indicate that, for reproduction to take place, another vitamin may be necessary. Animals deprived of this vitamin may thrive and be to all appearance perfectly well, but do not produce young. Conception takes place, but the embryo fails to attain full development, dies *in utero* and becomes absorbed. Vitamin-E is present in wheat-oil, butter and certain other fats. It is present in the unsaponifiable fraction, and is not destroyed by light, heat, acids, alkalis, oxidation or hydrogenation, or distillation *in vacuo*.

We have no conception of the mode in which the vitamins work. The minuteness of the quantities which are necessary shows that they can add no appreciable amount of energy to the body. They may act as catalysts.

THE NORMAL DIET OF MAN

Having learnt the significance of food in general and of the different food-stuffs in the animal economy, we are in a position to examine the actual requirements of the normal human individual. This involves a consideration not only of the total energy requirements of man according to age, size, sex and occupation, but also of the proper distribution of the foodstuffs in the diet.

We have seen that the energy requirements of a warm-blooded animal are a function of its surface. Knowing the weight and height of a man we can determine his surface by Du Bois' formula (p. 510). The average height and weight of English adults is 171 cm. and 70·3 kilos., corresponding to a surface of 1·8 square metres. The basal metabolism of a man is equal to 40 Calories per square metre per hour, so that the average man will have an hourly basal metabolism of 71 Calories. This is the energy output in bed and during sleep. When he is taking food this amount must be increased by about 10 per cent., and if he is up and about a further increase in metabolism will be evoked by the muscular movements, exposure to cold, &c. If we divide the twenty-four hours into three portions—eight hours' sleep, eight hours awake and eight hours' work—we must allow the basal metabolism for the eight hours' sleep, basal metabolism increased by about 30 per cent. for the eight hours during which the man is up and about

and taking meals, and the basal metabolism plus an additional amount for work during the eight working hours. It is by no means easy to decide what figure should be accepted as representing the average work of an adult man. It is usual to take this as involving an energy output of 1000 Calories. Of these Calories 20 per cent., or even more, may under favourable conditions be transmuted into mechanical work, so that 1000 Calories would be sufficient to provide for the performance of about 100,000 kilogrammetres of external work. With these assumptions we arrive at the following energy requirements for an adult working man :

8 hours' sleep at 71 (Basal Metabolism)	568 Calories.
8 hours awake at 92 (Basal Metabolism plus 30 per cent.)	736 „
8 hours' work (Basal Metabolism plus 1000 Calories)	1568 „
Total	2872 „

Some additional expenditure of energy will be involved in travelling, so that we are justified in accepting the figure usually given for the energy output of an average working man as 3000 Calories. It must be remembered that this figure is only an average—that is to say, it applies to a man of average size and weight and doing a certain amount of work. A small man will require less and a tall man more. A man in sedentary employment—*e.g.* typewriting, clerking, &c.—may not expend more than 200 to 400 Calories in the performance of external work ; mental exertion causes no appreciable rise in the metabolic exchanges. Such a man would therefore have a total energy output of not more than 2400 Calories a day. On the other hand, a heavy worker, such as a navvy, may easily expend 2000 or more Calories a day in the performance of external work. It is not surprising, therefore, that investigation of the diets actually in use among different classes of men shows very wide divergencies. An examination of the actual energy output as measured by the CO₂ excretion during work gave the following approximate energy requirements for men in different occupations :

Occupation.	Energy requirements (Cals.).
Tailor	2500
Bookbinder	2800
Shoemaker	2850
Metal worker	3200
Painter	3250
Carpenter	3200
Stone mason	4400
Woodcutter	5000

The energy requirements of women will show corresponding variation according to occupation, but will be in general less in consequence of their smaller size and surface. Du Bois has shown that, in addition to the influence of size, women have a lower basal metabolism per square metre of surface, *viz.* 37 Calories per hour as against 40 in the case of men. The average height and weight of Englishwomen are 159.3 cm. and 55.7 kilos., corresponding to a surface of 1.511 square metres and to an hourly output of 56 Calories. In estimating the total energy requirements of an average woman, we may reckon her work as two-thirds that of a man and as involving an expenditure of 660 Calories per day. We then arrive at the following Table for the energy requirements of the average woman :

8 hours' sleep at 56	448 Calories.
8 hours awake at 73 (Basal Metabolism plus 30 per cent.)	584 „
8 hours' work (Basal Metabolism plus 660 Cals.)	1108 „
Total	2140 „

It must be remembered that a woman's work is rarely finished when she goes home from her occupation, so that a certain amount ought to be reckoned for housework. We shall not be far wrong then, in accepting the usual estimate of a woman's requirements as four-fifths of those of a man, viz. 2400 Calories. Here again it must be remembered that this is merely an average figure, and that the requirements of different women correspond to their occupation and environment, and may vary from 1800 Calories up to 3000 Calories, or even more.

In children a computation of the energy requirements is rendered more difficult by two factors. In the first place the processes of growth are attended with an active metabolism, so that the metabolism is more energetic in the young animal than in the adult, even if we take into account the relative surfaces in the two cases. Thus the basal metabolism per square metre in boys of varying ages was found by Du Bois to be as follows :

Mean age.	Basal metabolism, Cals. per square metre per hour.
6.5	57.5
12.6	50.4
13.7	49.4
16.5	43
19.25.	40.7

In addition to this increased basal metabolism, if the processes of growth are to occur normally, there must be an excess of matter taken with the food over that excreted, since the growing animal is always putting on weight. Between the ages of eleven and sixteen both sexes put on weight at about 4 kilos. a year, which is equivalent to adding to the body a store of about 800 Calories per month. The second difficulty is due to the fact that, while children do not perform any measurable work, they are in a constant state of muscular activity, and this aimless activity of a child is of great value in procuring its healthy nervous and muscular development. The degree of this activity seems related to the amount of food taken—the increased energy of a child directly after a meal is a familiar phenomenon. If food is withheld or diminished this activity declines, but in this way energy is saved and the whole of the lessened food may go to maintain the temperature of the body and the normal processes of growth.

We may thus obtain a development of the child not differing appreciably from the normal on widely varying amounts of food, and it becomes difficult to say what is the average or the optimum amount that a child should have. Judging from the analysis of the food actually taken in the families of working men and others in receipt of sufficient incomes, it would appear that the amounts laid down by Lusk do not err on the insufficient side, although they are far less than are actually given in many well-to-do families and in high class schools, where great importance is attached to games and other forms of exercise. Lusk expresses the requirements of the different classes and ages in terms of the 'average man' taken as 1.

Class.	Coefficient.	Energy requirements (Cals.).
Average man	1	3000
Average woman	0.83	2500
Children, 0-6 (both sexes)	0.5	1500
" 6-10 " "	0.7	2100
" 10-14 " "	0.83	2500
Girls, 14 upwards	0.83	2500
Boys, 14 upwards	1	3000

These figures represent the actual energy *output* of the average individual, and are therefore equivalent to the food which must be digested and absorbed

from the alimentary canal in order to make good the loss. No food undergoes complete digestion, the average loss being about 10 per cent. with an ordinary mixed diet, as is shown in the following Table :

	Percentage of Foodstuffs Absorbed.				
	Protein.	Fat.	Carbohydrate.	Ash.	Total Energy.
Average of 5 experiments .	92·6	94	97·7	77·4	90·5

Three thousand net Calories (*i.e.* energy requirements) require therefore an intake of food with a Calorie value of 3300. The table of *food* requirements for various ages and sexes will be as follows :

Children, 0-6 .		1650 Calories.
" 6-10 .		2300 "
" 10-14 .		2750 "
Females, 14 and upwards .		2750 "
Males, 14 and upwards .		3300 "

If the food consists mainly of vegetable products it may be necessary to increase still further the allowance for loss in digestion, since on a diet such as rye bread as much as 33 per cent. of the total energy of the food may be lost in the fæces.

These values are for average well-nourished individuals. It has already been pointed out that in a state of semi-starvation, accompanied by loss of weight, the basal requirements may be reduced considerably. As a result of a number of experiments Chittenden came to the conclusion that there was a definite advantage to be gained by reducing not only the protein intake of the body but also the total food. Although such a limitation of the diet may be advantageous in a certain number of cases, there is no evidence which would warrant its general application; and the experience of Germany during the last three years of war has shown that a forced limitation of food to about two-thirds of what we have put down as normal, has resulted finally in a decrease of efficiency of mind and body and in a marked diminution in the resistance to infection, especially tuberculosis.

DISTRIBUTION OF FOODSTUFFS IN A NORMAL DIET

A Committee of the Royal Society has laid down the following as a proper diet for the 'average man' :

Protein.	Fat.	Carbohydrate.	Total Energy value.
100 grammes	100 grammes	500 grammes	3400 Calories

Wide variations are possible in the relative proportions of the foodstuffs without injury to health. It is important, however, to consider the limits within which these variations are permissible.

Proteins. As a rule an average mixed diet with a Calorie value of 3300 will contain about 100 grammes of protein. If the diet is mainly vegetable the proportion of protein will tend to fall. We have already seen that a certain amount of protein is essential to replace tissue waste. This amount may be determined by finding the minimum quantity on which nitrogenous equilibrium can be maintained, while the Calorie needs of the body are sufficiently satisfied at the expense of carbohydrate and fat. Under these conditions it has been found that 35 to 40 grammes of protein may suffice. In these experiments the protein was largely milk protein. Where animal protein is entirely absent from the food, a larger amount of vegetable proteins will be necessary, since they are of lower 'biological value'; and it is safe to lay down as a rule that for an average man the protein ration should not be diminished below 70 grammes per day. This should include different kinds of protein and if possible a certain proportion of animal protein, so as to ensure that all the essential amino-acids are supplied in the food.

Some authorities have recommended the diminution of protein to the minimum amount on the idea that the kidneys and other organs may suffer from the strain of eliminating excess of nitrogenous waste products. But the energy metabolism of protein results almost entirely in the formation of urea, an innocuous substance, which can have little harmful effect on the kidneys, even if we make the unjustifiable assumption that these organs, unlike other organs of the body, suffer as a result of their normal functional activity.

Carbohydrates are as a rule the most abundant and cheapest constituents of any diet, and form the greater part of vegetable diet. Only in the arctic regions may there be a lack of this constituent of the diet. A certain amount of carbohydrate is essential for man. We shall see later that sugar is always present in the circulating blood and is necessary for the normal functioning of the tissues, especially of the muscles. In the absence of carbohydrate in the food this sugar is manufactured by the body out of protein. Moreover under the same circumstances there is a deficient oxidation of the fats, so that the half-oxidised products of fat metabolism accumulate in the body, giving rise to acid intoxication. However, in temperate climates a shortage of carbohydrates can arise only under artificial conditions, and no need exists for laying down a minimum.

Fats can be produced by the animal body from carbohydrate. It would thus seem that, given sufficient carbohydrates in the food, there should be no absolute need for fats in the diet. It is stated by Hindhede that a man can be kept alive and can work normally on a diet in which fat is practically absent. In such cases it is essential that plenty of green food be provided in order to supply the fat-soluble accessory substances normally contained in the fats of milk and of meat. This statement may be true, but it is certain that it cannot be applied to all human beings. In practice we have to provide for each race a minimum desirable quantity of fat, which will differ in different races and be larger in northern than in southern races. Thus the Japanese soldier is content with 20 grammes of fat daily, while in our country the average man would not be content with less than 75 grammes of fat per day. Seventy-five grammes of fat has a Calorie value of about 680—i.e. nearly 25 per cent. of the daily requirements, and we may conclude as a general rule that one-fourth of the total energy of the diet should be supplied in the form of fat.

There are probably three reasons for this craving for fat. In the first place, fat is easily assimilated and is almost entirely absorbed in the alimentary canal; but whereas the greater part of the carbohydrate food is absorbed three hours after food has been eaten, the chief absorption of fat occurs between five and six hours after a meal. On this account a meal lacking in fat is deficient in staying power, and individuals deprived of fat get hungry some time before the next meal. The lumbermen of Canada satisfy their huge needs in Calories—6000 to 8000 a day—by a diet in which the fat represents 35 to 40 per cent. of the Calories.

In the second place, the bulk of food must be of considerable importance, especially when the total energy need of the body is very large. Weight for weight, fat has more than double the Calorie value of starch and sugar. But the difference in bulk is still greater, since fat is taken in a pure form, whereas the other foods are all mixed with a considerable proportion of water. The proteins in meat form only 15 to 20 per cent. of the total bulk. Starch cannot be taken dry. When ordinarily cooked it is swollen up with probably five to ten times its amount of water. Even after absorption the same necessity for increasing the bulk of carbohydrates with water persists. In adipose tissue there may be as much as 80 per cent. of fat. When carbohydrate goes into the circulation it is changed into sugar, and as sugar it needs

twenty times its weight of water to carry it. It acts, therefore, to some extent in the same way as common salt. Just as an extensive diet of salt may produce dropsy, so a diet of carbohydrate increases in the first place the water content of the body, and this factor, when associated with inanition and fat shortage, may itself produce actual dropsy. The question of bulk is probably one of the most important factors in determining the need for fat. The human alimentary canal, at any rate in the races of Western Europe, has been developed so as to cope with a diet in which 20 to 25 per cent. of the energy is presented in the form of fat. In order to get the same energy from carbohydrates the alimentary canal would have to be much larger. Although theoretically the absence of fat can be made up by an increased supply of carbohydrates, this can be carried out only in a certain number of individuals and under certain conditions. The ordinary individual deprived of fat diminishes his total intake of food and exists on a lower metabolic level. It is a notable fact that during the shortage of fat in this country in 1918 there was no appreciable increase in the consumption of cereals.

In the third place, carbohydrates are more subject to fermentative changes in the intestines than fats. Overloading the intestines with carbohydrates in many individuals leads to abnormal fermentation, the production of gases, and general discomfort. We may conclude then that, although man can dispense with fat, yet to develop his full efficiency as a working machine, fat is an essential ingredient of his diet and should furnish not less than 20 to 25 per cent. of the total energy of his food.

The Significance of Meat. Butcher's meat, according to the cut, contains from 15 to 20 per cent. protein, and from 15 to 30 per cent. fat. Its importance in the dietary is greater in northern latitudes and the protein of such a diet will be considerably more than is required for the mere repair of tissue waste. Under these conditions the fate of proteins in the body is somewhat different from that of the fats and carbohydrates. Proteins are not stored up in the body of the adult, but are burnt up in proportion as they are supplied in the food. Every protein meal therefore raises the production of heat in the body, and this production of heat is in addition to the heat which is produced by any muscular work undertaken at the same time. A large meat diet, apart from its content in fat, is of no special advantage for the performance of muscular work, and is a distinct disadvantage when this work has to be accomplished at a high external temperature. On the other hand, a diet in which there is a large proportion of meat is of value to men in sedentary occupations in a cold or temperate climate, since it enables them to maintain their body temperature without the necessity of bodily exercise. The idea that the heavy worker requires a large supply of butcher's meat is of doubtful foundation, though there is no doubt that in occupations involving exposure to cold and wet, a large supply of meat will add to the comfort of the individual by keeping him warm.

One other fact is of importance in this connection. Meat is not only easily cooked and presented in a palatable form, but its flavour renders other kinds of foods acceptable. It is thus habit rather than strict physiological principles which will probably govern the quantity of meat regarded as desirable in the normal diets of such people.

The Significance of Sugar. Sugar is the only food which is chemically purified before forming part of the diet. As a source of energy to the body it is nearly equivalent to an equal weight of starch. Its taste, however, renders it of value by increasing the palatability of other foods, and on this account a sufficient supply of sugar should be available for those classes whose facilities for cooking are defective. Sugar is readily absorbed from the alimentary canal and is the most useful food for sustaining muscular effort.

We thus see that a dietary to maintain a man in health and efficiency must fulfil the following requirements:

- (1) It must have a sufficient Calorie value (3300 for the average man).
- (2) It must contain protein, fats and carbohydrates. The quantity of each of the first two should be not less than 70 grammes a day. The protein should include a certain amount of animal protein.

(3) It should include a certain proportion of fresh foods, such as green vegetables, meat and eggs, and, in the case of children, milk, in order to supply the necessary accessory food substances.

(4) It must contain a proper proportion of the salts, especially sodium, calcium, potassium, chlorides and phosphates.

(5) It must be palatable. Appetite is an essential factor for the secretion of the digestive juices and therefore for the digestion and assimilation of the food, so that good cooking becomes an important condition for the maintenance of health. The use of various flavouring agents and condiments, which is general throughout all races, is therefore physiologically justified.

ALCOHOL. When alcohol is taken by man in moderate quantities, up to 10 c.c. per hour, the greater part of it undergoes oxidation and leaves the body as carbon dioxide and water. About 2 per cent., which escapes oxidation, is excreted unaltered by the lungs and kidneys. This oxidation of alcohol is a result of true utilisation, since the addition of a certain amount of alcohol to the food does not result in an increased output of carbon dioxide. Alcohol can, in this way, act as a food and supply up to 40 per cent. of the daily calories, provided it is taken in small doses, often repeated, so as not to result in there being a high alcohol content in the blood (E. Mellanby). When taken in large doses, this function is overshadowed by the poisonous action of the substance. A man unaccustomed to its action cannot take more than 16 to 25 grammes without experiencing its poisonous effects. Its value in a diet is chiefly that of an accessory or adjuvant, in exciting appetite by its taste and smell.

CHAPTER XXVIII

THE PHYSIOLOGY OF DIGESTION

CHANGES UNDERGONE BY THE FOODSTUFFS IN THE ALIMENTARY CANAL

THE use of the processes of digestion is to alter the foodstuffs so as to fit them for absorption into the blood, by means of which they may be carried to all parts of the body. In most cases the foodstuffs cannot be utilised in their original form by the living cells, but as we ingest them are in the most inactive form possible. Practically all are colloidal, neutral, and tasteless, and present no tendency to unite with oxygen or indeed to undergo any change whatsoever, apart from the interference of living organisms such as bacteria. In a starving animal the stores of carbohydrate and fat and the protein structure of the inactive living cells have to be converted into a soluble form—transformed, so to speak, into currency—before they can be utilised by other living cells, such as those of the heart, for the discharge of their normal functions and the maintenance of the life of the animal. In the same way, when we take these colloidal or insoluble substances into our alimentary canal, they have to be rendered soluble or diffusible, in order to allow of their easy transference across the wall of the gut into the blood and their transport to the tissue cells. The cells of the body cannot deal with all kinds of carbohydrate. Most animal cells will starve when presented with starch, dextrin, or any of the disaccharides, such as maltose, lactose, or cane sugar. It is necessary, therefore, that all the carbohydrates shall be reduced in the alimentary canal, or in its walls, to the form of monosaccharides. As regards proteins, the processes of digestion have a different significance, according as we are dealing with their value as sources of energy or as material for building up living protoplasm. If the proteins of the food are to be oxidised and utilised as a source of energy, they must be rendered soluble, so as to enable them to be absorbed and carried to those parts of the body where they may undergo deamination and complete oxidation. If they are to be built up as integral parts of living cells, to take the place of molecules which have been destroyed in the wear and tear of functional activity, the change must be almost equally profound. The proteins of the cells from different parts of the body have different molecular constitutions. Not only do they differ among themselves, but they differ very largely from many of the proteins which may be taken in with the food. A child is able to obtain material for the growth of his brain cells, his muscle cells, or his liver cells, from a diet containing protein in the form of caseinogen, or of vegetable gluten, or of meat fibrin. A reference to the Table on p. 60 will show the striking difference in composition between the various proteins of the food and the proteins which have to be formed from them in the living tissues. It is evident that to form serum albumin, for instance, out of wheat gliadin, an entire reconstruction

is necessary. This can only be accomplished by taking the protein molecule to bits, and by selecting certain of its constituent parts and building these up in the proper proportions to make a new protein molecule. This process of resynthesis must be carried out in the tissue cells themselves.

In primitive alimentary canals, every cell lining the canal may be endowed with amoeboid properties and capable of devouring the food particles, the subsequent changes in the latter to fit them for their journey through the rest of the body being performed in the body of the cell itself. In all the higher animals however, including ourselves, the greater part of the preparation of the food is accomplished extracellularly in the lumen of the alimentary canal by means of special digestive juices, which are formed by the activity of masses of cells produced as outgrowths from the wall of the canal. The digestive juices attack the foodstuffs by means of enzymes, and the action of these is hydrolytic, the foodstuffs taking up one or more molecules of water and undergoing dissociation into simpler molecules. Since each class of foodstuff requires a different enzyme, a great variety of these is concerned in the processes of digestion.

As the end result of digestion the many kinds of food taken by man are reduced to a fairly small number of simpler bodies. These end-products are :

(1) *Carbohydrates*. The monosaccharides: glucose, fructose, and galactose.

(2) *Fats*. Fatty acids or (in alkaline medium) soaps, and glycerol.

(3) *Proteins*. Here we have a great variety of mono- and diamino-acids, which may be enumerated as follows :

MONO-AMINO-ACIDS

Glycine (amino-acetic acid)	.	.	.	.	.	} Monobasic acids of fatty series
Alanine (amino-propionic acid)	.	.	.	.	.	
Serine or oxyalanine (oxamino-propionic acid)	.	.	.	.	.	
Amino-valerianic acid	.	.	.	.	.	
Leucine (amino-isobutylacetic acid)	.	.	.	.	.	
Isoleucine (amino-caproic acid)	.	.	.	.	.	} Dibasic acids
Aspartic acid	.	.	.	.	.	
Glutamic acid	.	.	.	.	.	
Phenylalanine	.	.	.	.	.	} Benzene derivatives
Tyrosine (oxyphenyl alanine)	.	.	.	.	.	
Proline (pyrrolidine carboxylic acid)	.	.	.	.	.	} Heterocyclic compounds
Hydroxyproline (hydroxypyrrolidine carboxylic acid)	.	.	.	.	.	
Tryptophane (indolamino-propionic acid)	.	.	.	.	.	

DIAMINO-ACIDS AND THEIR COMPOUNDS

Lysine (diamino-caproic acid)	.	.	.	.	.	} The 'hexone bases'
Arginine (guanidinamino-valerianic acid)	.	.	.	.	.	
Histidine (iminazol alanine)	.	.	.	.	.	
' Diamino-trioxydodecoic acid '	.	.	.	.	.	} Derived from a 12-carbon acid
Cystine (derived from amino-thiopropionic acid)	.	.	.	.	.	
						Sulphur-containing body.

Those constituents of the food, such as the water and salts, which undergo no metabolic alteration in the body, pass along the alimentary canal practically unchanged; if absorbed they pass without further alteration into the blood.

DIGESTION IN THE MOUTH

It is common experience that, when food is taken into the mouth, there is a flow of a liquid, 'saliva,' into this cavity. Saliva is the product of

secretion from three pairs of large salivary glands situated in the neighbourhood of the mouth and pouring their secretions into this cavity by means of ducts. It is possible to collect the fluid secreted by each of these glands separately ; and it is found that the saliva varies in properties according to the gland from which it is derived. In addition to these large glands the whole mucous membrane of the mouth is beset with small glands, the buccal glands.



FIG. 290. Dissection to Display the Salivary Glands.

- a. Sublingual gland.
- b. Submaxillary gland.
- c. Parotid gland.
- d. Common opening of ducts of submaxillary and sublingual glands.
- i. Opening of duct of parotid gland.

The saliva is in most cases a mixture of the secretions of all three pairs of salivary glands as well as of the small glands of the mucous membrane. When collected it forms a colourless cloudy liquid, slimy in character. The cloudiness is due to the presence of a number of formed elements consisting of desquamated epithelial cells, disintegrating leucocytes and gland cells, as well as coagulated clumps of mucin. Its reaction as secreted is neutral, or very nearly so (pH 6.8—7.0). On standing or heating it loses CO_2 and becomes alkaline and turbid from deposition of calcium carbonate. Its specific gravity varies between

1002 and 1008. Its chief constituents are coagulable proteins, mucin, and in some cases a diastatic enzyme, ptyalin, and traces of potassium thiocyanate, urea, &c. Its average composition in man is as follows :

Water	99.4				
Solids	0.6	Organic solids	0.4	Mucin	0.3
		Inorganic ash	0.2	(Chlorine	0.05)
				(P_2O_5	0.06)
				(Insoluble	0.03)

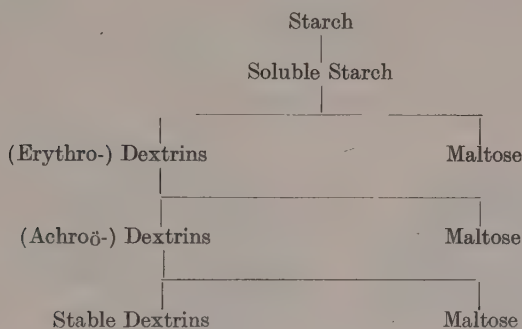
Freezing-point (Δ) = -0.07° to $-0.34^\circ C$.

Potassium thiocyanate is an almost constant constituent of human saliva, though it is often absent in that of other animals, such as the dog. It is generally present to the extent of .01 per cent., so that on the addition of a drop of ferric chloride to saliva a definite red colour is obtained. So far as we know it is formed in the body whenever cyanides or organic nitrites in small quantities make their appearance in the circulating fluid, either as the result of administration or perhaps as by-products in the normal processes of metabolism. The conversion of the poisonous cyanides into the almost innocuous thiocyanates seems to be a means by which the organism protects itself against the poisonous effects of the former. The channels of excretion of the thiocyanate are by the salivary glands, the kidneys, and possibly by the gastric juice.

THE USES OF SALIVA

The main function of saliva is to moisten the food and so facilitate its mastication and deglutition. The presence of the mucin is of special value for the latter process since it renders the mass of food slippery. In animals such as dogs, where the saliva is devoid of any digestive enzyme, this must represent its sole function. In man and some of the herbivora the saliva contains the enzyme ptyalin, which exerts a well-marked digestive effect on starch. If a warm solution of starch be taken into the mouth, kept there for one minute, and then expelled into a test-tube, the starch will be found to

have entirely disappeared, its place being taken by a reducing sugar. The stages in the action of saliva on boiled starch can be followed more easily when a very small amount of saliva is added to some starch solution at 37° , and portions of the digest are tested at intervals. The first change is a conversion of the opalescent gelatinising starch solution into a clear solution which no longer sets on cooling, but still gives a blue colour with iodine. The fluid contains what is known as soluble starch. The soluble starch then undergoes hydrolytic dissociation into a dextrin, which gives a red colour with the iodine and is therefore known as erythrodextrin, together with maltose. The erythrodextrin is then hydrolysed into an achroödextrin (giving no colour with iodine) and maltose, and the achroödextrin is still further broken up into stable dextrin and maltose. The conversion of starch into maltose by ptyalin ceases when 80 per cent. of the starch has been so converted, the remaining 20 per cent., called stable dextrin, being resistant. The stages in the conversion are represented in the following Table :



The process by which the huge starch molecule is converted into dextrins and maltose is a very complicated one, and a number of intermediate compounds of dextrins and maltose may exist between those whose presence is revealed by their varying reaction to iodine. On very prolonged action of saliva, some of the maltose formed is further hydrolysed to glucose, but this action is too slow to be of any importance in the body.

Ptyalin is most active in a neutral medium, so that the addition of minute traces of acid to an alkaline saliva increases its diastatic power. In the presence of free mineral acid, ptyalin is rapidly destroyed, 0.003 per cent. hydrochloric being sufficient for this purpose. Removal of salts by dialysis renders it almost or quite inactive, the activity returning when the salts are restored. Addition of small amounts of chlorides greatly accelerates the action of saliva. It acts most rapidly at 45° , but even at 0° C. its action is still just perceptible. If heated to 60° C. it is destroyed.

We have seen that boiled starch solution is changed by saliva when kept only a few seconds in the cavity of the mouth. When the starch is in the solid condition, as in biscuits and most farinaceous foods, its stay in the mouth during the normal process of mastication is not long enough to allow of any considerable hydrolysis occurring. When a meal is taken, the food which is swallowed forms a mass lying in the fundus of the stomach. This mass is penetrated only slowly by the acid gastric juice which is secreted by the glands of the stomach within five minutes of the taking of food. Even half an hour after a meal the interior of the mass of food in the stomach may be still found to be neutral or slightly alkaline. The food, therefore, thoroughly moistened by and mixed with saliva, remains in the

stomach for thirty to forty minutes before the salivary enzyme is destroyed by the penetration of the acid gastric juice. During this time the ptyalin continues to exert its effect, so that we may say that the chief part of the salivary digestion occurs actually in the stomach, and results in an almost complete alteration of the starch into dextrins and maltose. Thirty to forty minutes after a meal the food becomes thoroughly soaked with the acid gastric juice, and salivary digestion gives place to gastric digestion.

THE SECRETION OF SALIVA

The greater part of the saliva is formed in man by three pairs of glands, viz. the sublingual and the submaxillary glands, situated in the floor of the mouth below the jaw, and the parotid gland, lying in the cheek over the ramus of the inferior maxilla.

The arrangement of these glands, especially of those in the floor of the mouth, varies somewhat in different animals. In the dog and cat, the sublingual gland is wanting, its place being taken by a gland situated somewhat further back and known as the retrolingual gland. In the pig both retrolingual and sublingual glands are present in addition to the submaxillary, and one may sometimes find traces of the retrolingual gland in man. Many animals, e.g. the dog, also possess a gland situated in the orbit,



FIG. 291. A. Serous Gland. B. Pure Mucous Gland from Mouth. (KÖLLIKER.)
a. Ducts. f. Fat cells.

which pours its secretion into the mouth—the orbital gland. These glands can be divided, according to their structure and the nature of the secretion which they form, into three classes. Among the small buccal glands we may distinguish two types, the *mucous gland* and the *serous gland*. In specimens hardened and stained by the ordinary methods, the mucous gland is distinguished by the fact that its short duct opens into wide alveoli, the lining cells of which are distended with mucin and therefore present a clear unstained space in the section. In the other type, the serous gland, the duct lined with columnar cells branches into a series of acini, which present a well-marked lumen and are lined with small granular cells with a very distinct and well-staining nucleus. The same general distinction can be made out in the large salivary glands. The parotid gland in man and in all the higher mammalia is a typical serous gland, though here and there a mucous cell may be occasionally seen. The orbital gland of the dog resembles one of the mucous glands of the general mouth cavity on a large scale. The sublingual and submaxillary glands in man represent a third type called *mixed* glands. Most of the alveoli are mucous in character. At the ends of the alveoli are seen crescent-shaped serous cells between the mucin-distended cells and the basement membrane. These are known as the *demilune cells*, or the *Crescent cells* of Gianuzzi. In some cases these mucous alveoli with demilunes may be found alongside of typical serous alveoli.

Thus in man the submaxillary gland is usually a mixed gland, the serous alveoli predominating. The sublingual gland is also mixed, but with a predominance of the mucous alveoli. In the monkey the submaxillary gland is almost entirely serous. In the dog the submaxillary gland is a pure mucous gland with demilunes, while the retrolingual and sublingual glands when present are of the mixed type. In the rabbit the submaxillary gland is serous, while the sublingual gland is mucous. In the cat

the submaxillary is mucous, the retrolingual is mixed, and the sublingual, when present, is mixed, with predominance of the mucous type.

The secretion of the separate glands in man can be studied by passing a fine catheter into the appropriate duct, and also in certain rare cases where fistulæ occur in the parotid duct. The normal behaviour of the salivary glands during digestion is best studied by aid of a method used long ago by de Graaf and reintroduced with considerable elaboration of late years by Pavlov. It is possible, without any disturbance of the animal's nutrition, to transplant the papilla, on which the duct opens, to the outside, so that the saliva from any particular gland shall flow externally instead of into the cavity of the mouth. These fistulated glands retain their normal structure and functions for many months, though sometimes, after about a year, the gland slowly becomes fibrotic. By attaching a small funnel to the fistulous opening, it is easy to collect the pure saliva, unmixed with the secretion of any other of the glands.

By this method it has been found that the glands are not continually secreting; as soon as food is introduced into the mouth there is a secretion of saliva, the relative extent to which different glands are involved varying according to the nature of the stimulation. Thus with meat and other moist foods there is only a small amount of secretion, which is derived chiefly from the submaxillary and sublingual glands, and is rich in organic constituents. When dry or undesirable material, such as dry powdered meat, or sand, is introduced, the flow of juice is more copious and more watery. Secretion may be produced in the dog by "psychic" excitation. Thus, salivation may be induced by showing food to the dog, or even by the suggestion that dry powder is to be introduced into the mouth. This is an example of a conditioned reflex.

The serous and mucous glands differ in the nature of their secretion. A serous gland, such as the parotid, gives a clear watery secretion almost free from mucin, but containing small traces of coagulable protein. The mucous gland delivers a secretion which is viscid from the presence of mucin, and contains also a small trace of coagulable protein. Both in parotid and mucous saliva the percentage of salts is very low. In the dog the saliva is free from any enzymes. In man ptyalin—the starch-splitting enzyme—is found in the saliva from both kinds of gland, though it is about four times as concentrated in that secreted by the parotid gland. The total amount of saliva which may be obtained varies of course in different animals. Each gland may, however, in the course of the day give an amount of juice far exceeding, *e.g.* ten or twelve times, its own weight. In man it is reckoned that over one litre of saliva may be formed every twenty-four hours, and in the herbivora, such as the horse, the total diurnal production must amount to many litres.

The activity of the salivary glands must be excited by reflex means. The afferent nerves in this reflex are those that supply the mucous membrane of the mouth, *i.e.* the fifth nerve and the glossopharyngeal. Each one of the large salivary glands receives efferent nerve fibres from two sources: from the cerebrospinal and from the sympathetic system. The central origin of the nerve supply is in a group of cells in the formatio reticularis between the nucleus of the VIIth and the nucleus of Deiters. From this point they diverge in their course to the glands. The fibres to the submaxillary, the sublingual, and the retrolingual glands pass into the facial nerve, and from this nerve along the chorda tympani to the lingual division of the fifth nerve. The lingual nerve passes below the duct, and just before it crosses the two ducts of the submaxillary and retro- or sublingual glands, it gives off a small branch backwards, the *chorda tympani*, which runs along the submaxillary duct to

be distributed to the glands, and in its course gives off fibres also to the retro lingual. (Figs. 292 and 293.)

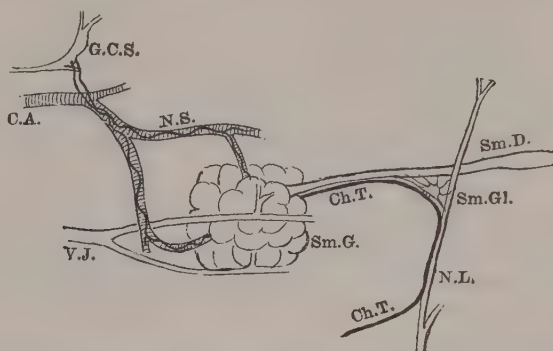


FIG. 292. Diagram of Nerve Supply to Submaxillary Gland. (After FOSTER.)

Sm.G.	Submaxillary gland.	V.J.	Jugular vein.
N.L.	Lingual nerve.	C.A.	Carotid artery.
Ch.T.	Chorda tympani.	G.C.S.	Superior cervical ganglion.
Sm.Gl.	Submaxillary ganglion.	N.S.	Sympathetic fibres ramifying on facial artery.
Sm.D.	Wharton's duct.		

Two neurones are involved in the cranial supply. By means of the nicotine method, Langley has shown that all the preganglionic fibres to the sublingual and the submaxillary glands end somewhere near the glands in connection with ganglion cells, from which non-medullated post-ganglionic fibres pass to the glands. These relay ganglia for the submaxillary gland are scattered cells lying in the hilum of the gland itself; in the cat those for the retrolingual gland are in the so-called 'submaxillary ganglion.' The fibres to the sublingual gland in man probably take a similar course. The fibres are apparently finally distributed to the secreting

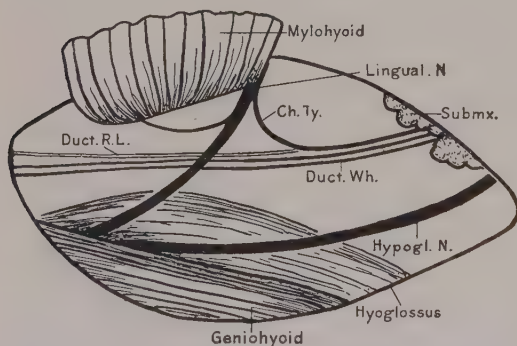


FIG. 293. Diagram of the Arrangement of the Nerve Supply to the Submaxillary Gland, as exposed in an actual experiment. (ALCOCK and ELLISON.)

Duct. Wh.	Wharton's duct (of submaxillary).
Duct. R.L.	Retrolingual duct.
Ch.Ty.	Chorda tympani nerves.

alveoli, where they end freely on the secreting cells just below the basement membrane.

The fibres to the parotid gland pass along the glossopharyngeal nerve and its tympanic branch (nerve of Jacobson) to the tympanic plexus, and then by the small superficial petrosal nerve to the otic ganglion, where relays occur, the post-ganglionic fibres then passing by the auriculo-temporal, which is a branch of the third division of the fifth nerve.

The sympathetic supply to all these glands is contained in fine filaments on the walls of the arteries with which they are supplied. The fibres are derived from the spinal cord, whence they issue by the upper three ventral thoracic nerve roots. They pass into the cervical sympathetic as preganglionic

fibres which end around the cells of the superior cervical ganglion, and a fresh relay of fibres, chiefly non-medullated, arises from the cells and travels on the walls of the branches of the external carotid artery to their destination.

The effect of stimulating the peripheral ends of the cranial nerves going to the glands presents a general resemblance, whichever be the gland involved. Within a period of half to two seconds after the stimulation has been applied, a secretion of saliva is produced, presenting similar characters to that which would be obtained from the gland under normal conditions. The concentration of the saliva, as well as its rate of secretion, depends on the strength of the stimulus. The following table (Heidenhain) shows the effect on the amount and composition of submaxillary saliva obtained by weak and strong stimulation of the chorda tympani nerve :

Strength of stimulus.	Quantity in one minute.	Per cent. of organic solids.	Per cent. of salts.
Weak	0.17	0.84	0.20
Strong	0.72	2.06	0.46
Weak	0.17	1.67	0.26

With the strong stimulus the amount of saliva was increased over four-fold, while the percentage of organic substances in the saliva was raised from 0.84 to 2.06 per cent. There was at the same time an increase in the percentage of salts. If the excitation be continued for a considerable time, there is a gradual rise in the percentage of inorganic salts and a fall in the percentage of organic matter.

The cranial nerves going to these glands have another important effect, namely vaso-dilatation. It was shown by Claude Bernard that on exciting the chorda tympani the flow from the vein of the submaxillary gland might increase four to eight times, and indeed to such an extent that the blood passing through the gland did not stay long enough to lose much oxygen. Moreover, the dilatation of the arterioles removes the normal resistance which serves to damp and obliterate the pulse between the arteries and the veins. As the result of exciting the chorda, therefore, the blood coming from the vein may show distinct pulsation, and may have a brilliant scarlet hue just as if it were derived from an artery. The same dilatation has been observed to attend excitation of the cranial supply to the parotid gland.

The effects of exciting the sympathetic nerve supply differ according to the gland and the animal which is the subject of experiment. In the dog excitation of the cervical sympathetic causes the secretion of a few drops of thick viscid saliva from the submaxillary gland. In this animal no secretion is obtained at all from the parotid gland on exciting the sympathetic, but the influence of the excitation is shown by the occurrence of histological changes in the gland cells. In the cat, the submaxillary saliva obtained on sympathetic excitation may be as copious as, and even more watery than, the saliva obtained from the submaxillary on stimulation of the chorda tympani. We shall have later on to discuss how far these results are to be ascribed to a fundamental difference in the point of attack of impulses carried to the secreting cells by the two sets of nerve fibres, and how far to the varying effects of the cranial and sympathetic nerves respectively on the blood vessels. It must be remembered that the sympathetic nerve

carries the vasoconstrictor fibres to most or all of the vessels of the head and neck, and therefore in most cases stimulation of this nerve causes vascular constriction in the gland affected. Before attempting to decide this point we must study in somewhat greater detail the changes which occur in the gland concomitantly with the secretion.

CHANGES IN THE GLAND ACCOMPANYING SECRETION

The fact that a submaxillary gland of the dog under favourable conditions will secrete its own weight of saliva in five minutes, and will on continued stimulation secrete for many hours afterwards, shows that there is a continual renewal of the fluid which is turned out in the secretion. If we refer to the diagrammatic representation of the elements which make up a secreting lobule and which may be involved in the act of secretion (Fig. 294), we see that between the lumen of the duct and the blood, which must be regarded as the source of the fluid, the following layers of cells intervene: (1) the endothelium of the blood capillaries; (2) the basement membrane; (3) the epithelial cells of the gland proper. We have in the first place to decide to which of these elements can be ascribed the chief part in the act of secretion.

The secretory activity of the submaxillary gland, however evoked, is usually associated with a considerable dilatation of the vessels of the gland, and a consequent large increase in the blood flow through the gland, which may amount to between three and eight times the quantity passing during rest. Such an increase in the supply of blood is necessary in order to afford a source for the large quantity of fluid which is turned out in the saliva. Another effect of the dilatation will be to raise the pressure in the capillaries of the gland. We cannot, however, regard this rise of pressure in the capillaries as an essential factor in the act of secretion. If atropine be administered, excitation of the chorda causes the

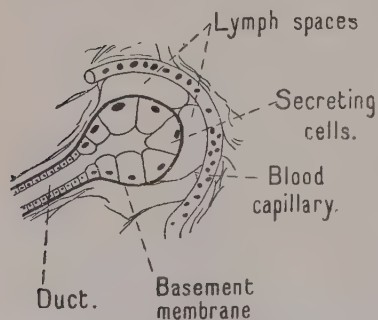


FIG. 294. Diagram to show Relation of the Secreting Cells of a Gland to the Blood and Lymph Supply.

same vaso-dilatation as before, though no secretion is produced. Moreover Ludwig showed that the force with which the secretion is turned out into the ducts of the gland is greater than that represented by the blood pressure. If two manometers be connected, one with the carotid artery and the other with the duct, it will be found that on stimulating the chorda tympani nerve the mercury will be driven up by the pressure of the secretion in the corresponding manometer until it attains a height which may be double that of the mercury in the manometer connected with the carotid artery, and therefore must be still greater than the pressure in the capillaries of the gland. This experiment, which is easy to repeat, showed the impossibility of the act of secretion being in any way determined by a process of filtration.

We have now further evidence that work is done in the production of the salivary secretion. When a fluid containing salts in solution is filtered through a porous membrane, the filtrate has the same content in salts as the original fluid. We can effect a separation of dissolved salts from a fluid by filtration under pressure through some so-called semipermeable membrane.

Under these circumstances a very large pressure is necessary in order to cause the filtration of any fluid at all, a pressure greater than the osmotic pressure exerted by the substances in solution. Thus if we were filtering a 1 per cent. solution of NaCl through a semi-permeable membrane, we should have to exert a pressure of about seven atmospheres in order to obtain a filtrate free from sodium chloride. To obtain a filtrate containing half the amount of sodium chloride, if such were possible, would therefore need a pressure of about three and a half atmospheres. On comparing the osmotic pressures of saliva and blood respectively—using the depression of freezing-point as our index—we find that the osmotic pressure of saliva is between half and three-quarters that of the blood plasma. Supposing the membrane separating the lumen of the duct from the blood vessels could be regarded as a semi-permeable membrane, we should need, in order to effect the separation, a pressure ten to twenty times as large as the arterial blood pressure. We must conclude, then, that work, both

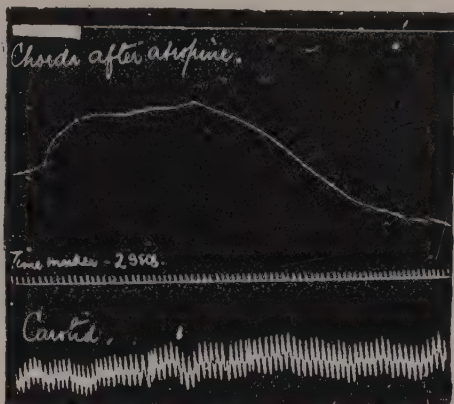


FIG. 295. Tracing of Volume of Submaxillary Gland, showing Effect of Stimulation of the Chorda after Administration of 10 mg. Atropine. The Blood Pressure (lowest line) was unaltered by the Stimulation. (BUNCH.)

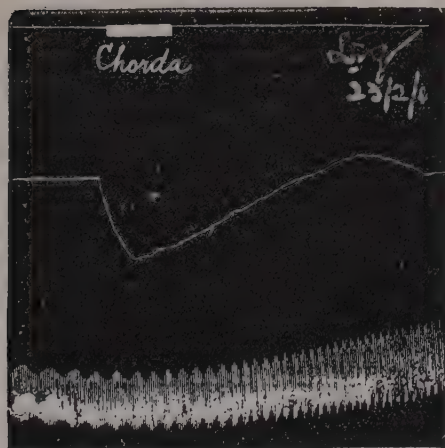


FIG. 296. Tracing of Volume of Submaxillary Gland, showing Decrease on Excitation of Chorda. (BUNCH.)

whole gland. By placing the gland in a plethysmograph we can record the actual changes in its volume which ensue on excitation of the chorda tympani. If all secretion be prevented by the previous administration of atropine, stimulation of this nerve produces, as might be anticipated, an increased volume of the gland in consequence of the dilatation of its vessels (Fig. 295). If, however, the gland be allowed to secrete, we obtain, in spite of the simultaneous increase in size of the vessels,

osmotic and mechanical, is performed in the separation of the fluid from the blood and its transference in the form of saliva to the duct.

A very simple experiment will suffice to show that this work must be effected, not by the endothelial cells of the blood vessels, but by the gland cells themselves. The fluid passes from the blood vessels first into the lymphatic spaces, whence it is taken up by the secretory cells. If the first act in secretion consisted in an increased exudation of fluid from the blood into the lymph spaces, the first effect of exciting the chorda tympani nerve should be to cause an accumulation of fluid in the lymph spaces, some increase in the lymph flow from the gland, and the swelling of the

an actual diminution in the size of the gland itself, showing that the first effect of the stimulation is on the cells of the alveoli (Fig. 296). Under the stimulus, these empty themselves of the fluid they contain, replenishing themselves at the expense of the fluid in the lymph spaces. The increased passage of fluid from blood to lymph space is therefore a secondary and not a primary effect of the nerve stimulation, and the first effect on the gland is a diminution of volume and not an increase, as one would expect if the vascular endothelium were primarily responsible for the act of secretion.

HISTOLOGICAL CHANGES DURING SECRETION

The process of secretion is associated with marked changes in the structure of the cells composing the secretory alveoli. The changes are of the same general character whatever class of glands we investigate, though the ease with which they are to be

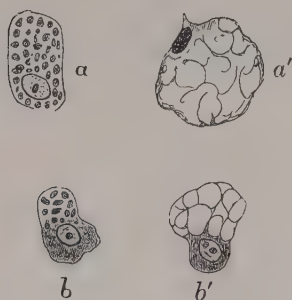


FIG. 297. Mucous Cells from a Fresh Submaxillary Gland of a Dog.
(LANGLEY.)

- a. Mucous cell examined fresh from a resting gland.
- a'. The same cell treated with weak alcohol.
- b and b'. Cells from a discharged gland before and after treatment with weak alcohol.

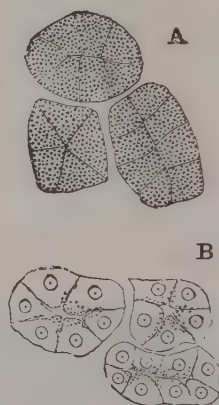


FIG. 298. Acini of a Serous Salivary Gland. (LANGLEY.)

- A. Resting condition.
- B. Discharged condition.

demonstrated varies with the effects on the various glands of the hardening fluids usually employed. If a small fragment of a mucous gland be teased in blood serum or in 2 per cent. NaCl solution, the cells are found to be packed with a mass of coarse, highly refractive granules (Fig. 297). If a corresponding specimen be made from a serous gland (Fig. 298), the cells are also packed with granules which, however, are much finer in structure. On making similar specimens from glands which have been forced to secrete for six or seven hours, the individual cells are found to be much smaller and the protoplasm of the cell is relatively increased in amount, while the granules are much fewer and are now confined almost entirely to the inner margin of the cell. Activity is thus associated certainly with a discharge of granules, and probably with some increased building up of protoplasm. We may regard the act of secretion as determined by the alteration of the granules and their discharge, together with water and salts, to form the specific secretion of the gland. During rest the granules are re-formed by precipitation in or modification of the protoplasm surrounding the nucleus. We have evidence that, although the granules form the secretion, they represent, not the secretion itself, but a precursor of some at any rate of its constituents. Thus if acetic acid be added to the saliva obtained from the submaxillary gland, the mucin is precipitated as threads and films. If the granules in the secreting cells also consist of mucin, we should expect acetic acid to have a coagulating effect upon them. We find on the contrary that, on allowing acetic acid to flow over a section of the fresh gland, the granules at once swell up and burst. We must regard these granules therefore, not as

mucin, but as a precursor of mucin, mucigen. The effect of ordinary hardening reagents, such as dilute alcohol up to 70 per cent. or Müller's fluid, is to cause these granules to swell up so that the cells become filled with a mass of mucin giving the typical hyaline appearance of ordinary sections of these glands. In the case of the serous glands the granules (Fig. 299) are apparently protein in nature. Where ptyalin is a constituent of the saliva, we are probably justified in assuming that it is contained either preformed or more probably as a precursor in the granules. In the glands of the stomach we have evidence that the granules are not pepsin—the characteristic enzyme of gastric juice—but a precursor of this substance, namely, pepsinogen. It is very customary therefore to speak of the granules in a secreting gland as *zymogen granules*, i.e. the precursors of zymins or enzymes. It is probable that we ought to regard these granules not merely as material precursors of the constituents of the secretion, but as little machines or cell laboratories in which proceed a whole series of chemical and osmotic changes, which determine the production of the fully formed secretion directly from the protoplasm and indirectly from the ordinary constituents of the surrounding lymph.

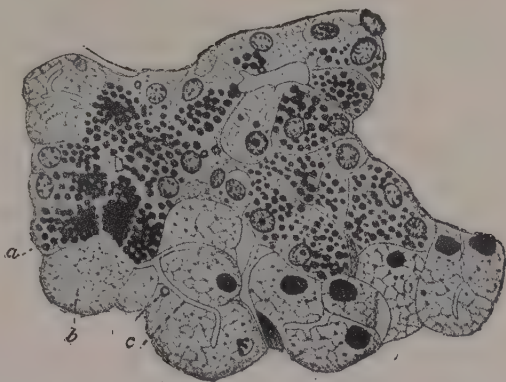


FIG. 299. Submaxillary Gland of Rabbit. (SCHAFER after E. MÜLLER.)

The cells, all serous, are in different functional states :

- a. A loaded cell.
- b. A discharged cell.
- c. A secretory canaliculus penetrating into a cell.

From an examination of the stained specimens of glands the following stages in the production of secretion have been described :

(1) In the neighbourhood of the nucleus, and probably with its active co-operation, a differentiation of the protoplasm occurs with the production in most cases of a basophile substance which in hardened specimens generally takes the appearance of filaments. Since these filaments are sometimes regarded as the active part of the protoplasm, they have been given the name of *ergastoplasm* (Fig. 300, c and d).

(2) By a modification of the ergastoplasm, granules are formed. After their first appearance these granules undergo gradual modification, as shown by the fact that the staining reactions of the granules near the base of the cell differ from those of the granules at the free margin.

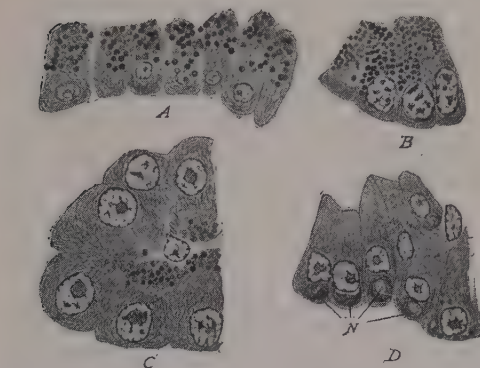


FIG. 300. Cells of Pancreas, showing Successive Stages in Activity, A, B, C, D.

A. Resting. D. Discharged gland. (MATHEWS.)

(3) When the secretion is excited, the fully formed granules take up water and salts in varying proportions, swell up, and discharge their contents into the lumen of the alveolus as the secretion proper to the gland.

ELECTRICAL CHANGES

Every localised chemical change in a system permeated by electrolytes must give rise to electrical differences of potential. It is therefore natural

that electrical changes should accompany the intense chemical activity which is associated with secretion. The interpretation of these changes is difficult, owing to the simultaneous operation of another factor which may determine electrical differences of potential, namely the movement of fluids through porous membranes. If the hilum of the submaxillary gland and its outer surface be connected with a galvanometer, a resting difference of potential is nearly always found, generally in such a direction that the outer surface is positive to the hilum. The current through the gland is therefore from within out. On exciting the chorda tympani nerve a diphasic effect is generally obtained, the resting difference being first increased and later on diminished. On excitation of the sympathetic nerve we generally obtain a purely negative variation of the resting difference. These results were interpreted by Bayliss and Bradford as due to the co-operation of the two factors, chemical change in the gland cells and movement of fluid through the cells. The positive variation, *i.e.* the current from within out, was ascribed to the movement of fluid, whereas the negative variation of the resting difference was thought to be due to the chemical changes in the gland cells.

THE SIGNIFICANCE OF THE DOUBLE NERVE SUPPLY TO THE GLANDS

According to Heidenhain, although the parotid gland gives little or no secretion on stimulation of the sympathetic nerve, prolonged stimulation of this nerve causes histological changes in the gland even more marked than those produced by the cranial nerve. Similar histological changes were found by him in the submaxillary gland. He was therefore led to put forward the hypothesis that the salivary glands are supplied by two fundamentally different classes of fibres, namely: (1) trophic fibres, which determine the chemical changes in the gland responsible for the production of the specific constituents of the secretion, and (2) secreto-motor fibres, excitation of which causes the cells to take up water and salts from the lymph and blood, and pass them in large quantities into the duct. According to this view the sympathetic nerve supply to the gland would consist almost entirely of trophic fibres, whereas secreto-motor fibres would predominate in the cranial nerve supply. The action of atropine would appear at first sight to favour this hypothesis. In minute doses it entirely annuls the action of the chorda tympani nerve or the corresponding nerve to the parotid, while it is without effect on the sympathetic nerve supply unless given in huge doses. The preponderating effect of the sympathetic on the histological structure of the gland cells has not been confirmed by later observers, and the varying effects of atropine on the two sets of nerve fibres may be conditioned by morphological rather than by functional differences between their nerve endings. According to Langley and Carlson, the difference in the action of the chorda tympani and of the sympathetic on the submaxillary gland is due to the opposite action of these nerves on the blood supply to the gland, the sympathetic causing vaso-constriction, and the chorda tympani vaso-dilatation; they find that clamping the carotid artery during chorda stimulation diminishes the amount of saliva secreted but increases the percentage of solids in the fluid. This theory is, however, inadequate to explain the differences observed in the secretion of saliva reflexly aroused by introduction of substances into the mouth. In a dog with a permanent submaxillary fistula a copious flow of saliva may be caused by the introduction of 0.25 per cent. hydrochloric acid or of meat powder. The amount of saliva secreted under the two circumstances is approximately the same, but that evoked by the introduction of meat powder contains about five times as much organic solids as that which follows the introduction of acid into the mouth. Babkin has shown that the same differences are found after complete section of the sympathetic and that there is the same acceleration of the circulation through the gland whether the secretion is aroused by introduction of meat powder or of acid. It is impossible, therefore, to explain the difference in the composition of the saliva obtained under these two circumstances as due to differences in the blood supply to the gland, and we must conclude either that the chorda tympani contains different kinds of fibres which are excited to varying extent according to the nature of the reflex stimulations, or that one and the same nerve fibre can convey specifically different impulses. The latter explanation

would not be in accord with the generally accepted Müller's law of specific irritability, but is the explanation to which Babkin himself inclines. At any rate it is certain that according to the nature of the reflex stimulus, either the secretion of water and salts or the secretion of organic solids may preponderate, altogether apart from changes in the circulation simultaneously evoked. It has also been found that simultaneous stimulation of the chorda tympani and sympathetic nerves gives rise to an *augmented secretion* of saliva, greater than that given by the chorda alone, although the blood flow through the gland is less. (GESELL.)

THE ENERGY INVOLVED IN THE ACT OF SECRETION

Barcroft has attempted to determine the total amount of energy set free by the gland in the act of secretion, by measuring its respiratory exchange under the conditions of rest and activity. He found that the resting submaxillary gland in a small dog took up 0.25 c.c. of oxygen per minute, while during active secretion it absorbed 0.86 c.c. O_2 . Assuming that the total oxygen taken up is employed in the oxidation of a food substance, such as glucose, and that the whole of the energy of the chemical changes is set free in the form of heat, we find that a resting gland weighing about 6 grammes produces about 1.1 calories per minute. We know, however, that a certain amount of external work is performed in the secretion of a saliva containing less salts than the original blood and also, when there is any resistance to the flow of saliva through the duct, in raising the hydrostatic pressure of the saliva in the duct to a height greater than that in the blood capillaries.

Can we from all these data form a conception of the total changes occurring in the gland and involved in the formation of the secretion? Even during rest, changes are going on in the gland cells, changes which involve the taking up of food material and its assimilation, under the influence of the nucleus, into the undifferentiated cytoplasm. In this cytoplasm a further change occurs, leading to the formation of granules. When activity is excited by the stimulation of secretory nerves, the primary change appears to involve simply the granules. These absorb water, apparently against the osmotic pressure of the surrounding cytoplasm. Those nearest the lumen swell up become converted into spheres containing water and salts in smaller proportion than exists in the lymph bathing the cells (and presumably in the protoplasm surrounding the granules), and in this swollen form are discharged or ruptured on the periphery of the cell into the lumen, so giving rise to secretion.

This discharge of a fluid with a smaller molecular concentration than the cell or surrounding blood plasma, must lead to an increased concentration in the remaining parts of the cell. The increased concentration would naturally induce a flow of water from lymph into cell, and the consequent concentration of the lymph would in the same way cause a flow of water from blood to lymph. This pull of water by the cell from the blood is still further increased in another way. The act of secretion, involving as it does the expenditure of energy, can be carried out only at the expense of chemical changes in the cell. These chemical changes, as in all other metabolic processes of the body, will result in the formation of a number of small molecules from the great colloid molecules of the protoplasm. The products of metabolism, or *metabolites*, will therefore accumulate in the cell, pass into the lymph, and increase the concentration of the latter. The increased concentration will call forth an increased transudation of fluid from the blood vessels, and the transudation thus evoked will be greater than that necessary to provide the water of the saliva, and will therefore produce a distension of the lymphatic spaces of the gland

and an increased discharge of lymph along its efferent lymphatics. As a secondary result of the activity, perhaps in consequence of the removal of the products of the resting metabolism of the gland, there is increased activity of the nucleus, and therefore a tendency to increased assimilatory changes and a preparation of the cell for further secretory changes, either immediately or hereafter.

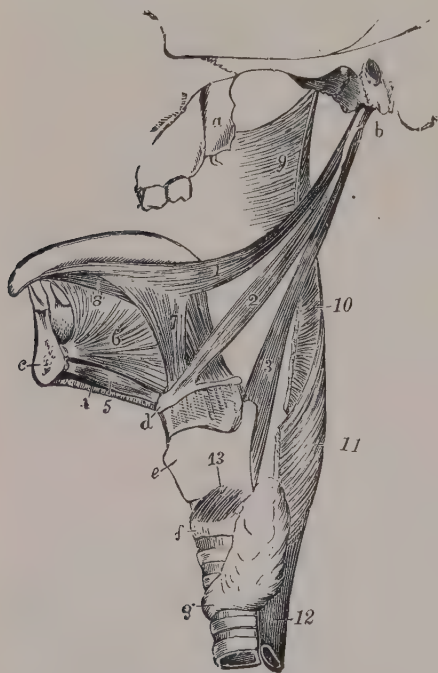


FIG. 301. Dissection to show Muscles Employed in Deglutition.

b, styloid process, from which arise 1, the styloglossus; 2, the stylo-hyoid; 3, the stylo-pharyngeal muscles; *c*, section of lower jaw; *d*, hyoid bone; *e*, thyroid cartilage; *g*, isthmus of thyroid gland; 4, cut edge of mylohyoid muscle; 5, 6, 7, 8, muscles of tongue; 9, 10, 11, superior, middle, and inferior constrictors of pharynx; 12, esophagus. (ALLEN THOMSON.)

in the living cell, we are brought up against insuperable difficulties, and any theories so far put forward merely serve to show how far we are still from the actual comprehension of the events occurring in every living cell and underlying its conditions of rest and activity.

DEGLUTITION

The food after mastication is carried to the stomach by a complex series of co-ordinated movements involving the muscles of the pharynx and the cesophagus (Fig. 301).

Various methods have been used to study the process of deglutition in man and the higher animals. Important information can be obtained by allowing a man or animal to swallow either a fluid or solid with which a bismuth salt or barium sulphate is mixed, and observing the passage of the opaque substance under the Röntgen rays. The sub-nitrate of bismuth may be mixed with milk for a fluid, or with bread and milk for a semi-solid substance, or may be enclosed in a cachet and swallowed as a solid bolus. The time of entry of the food into the stomach may be determined by auscultating with a stethoscope over the region of the cardiac orifice. Since a certain amount of air is always swallowed at the same time as the food, the escape of this air through the small cardiac orifice gives rise to a bubbling noise which can be easily heard. In the horse, the

It was shown by Pavlov that the amount of nitrogen in the saliva formed by the submaxillary gland when the chorda was stimulated was greater than the amount of nitrogen lost by the gland itself. Anrep has shown that during the process of secretion the rebuilding of mucigen either does not occur, or happens too slowly for detection, so that the mucin content of the saliva, on continuous chorda stimulation, steadily diminishes. The non-mucin nitrogen of the saliva is, however, not reduced on prolonged stimulation, and hence is being continually passed on from the blood and lymph. Replenishment of mucigen after complete exhaustion may take as long as three days, and appears to be slightly accelerated by extirpation of the superior cervical ganglion. The submaxillary gland uses glucose from the blood stream at a rate which is accelerated when the gland secretes. (ANREP and CANNAN.)

In the gland, as in muscle, when we attempt to form a conception of the mechanism of the chemical machine

movement of a bolus down the œsophagus can be seen or felt from the outside of the neck. The relative time relations of the events at different parts of the œsophagus may be obtained by passing sounds provided with rubber balloons to different levels in the tube and connecting these sounds with recording tambours or piston recorders. This method has been employed both in men and in animals.

When a mouthful of water is taken, two sounds may be heard on auscultating over the œsophagus. The first sound immediately follows the beginning of the act of swallowing and is probably due to the impact of the fluid against the posterior pharyngeal wall, brought about by the sudden contraction of the mylohyoid and other muscles which throw the fluid from the back of the tongue across the pharynx. The second sound is heard best by listening over the epigastrium. It begins from four to ten seconds after the first sound, and lasts for two or three seconds. The interval between the two sounds is not constant. If the observation be carried out on a man lying on his back, the trickling second sound is changed into a series of sounds which have been described as squirts, which vary from two to five in number, each lasting about one second. The second sound may be absent when a solid bolus is swallowed. On observing the process by Röntgen rays, very

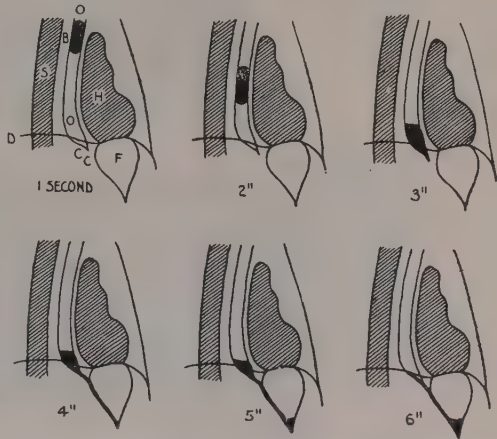


FIG. 302. Appearance of lower end of Esophagus and Cardiac Sphincter, at one to six seconds after swallowing; observed under X-rays. (HURST.)

much the same time relations are obtained. If a mouthful of milk mixed with bismuth carbonate be swallowed, it will be seen passing rapidly down the œsophagus to the cardiac orifice of the stomach. Here the passage becomes slow, and the fluid enters slowly in a narrow stream into the stomach. The average time which elapses between the beginning of deglutition and the disappearance of the last trace of fluid from the œsophagus is about six seconds (Fig. 302). The same course of events is induced when the food swallowed is semi-solid. If, however, the bolus be dry, such as a cachet, it may take as much as fifteen minutes to reach the cardiac orifice, although the individual who has swallowed it is quite unaware of its continued presence in the œsophagus. If, as would normally be the case, the cachet be well moistened with saliva or water before swallowing, it passes much more rapidly.

It has been customary since the time of Magendie to divide the act of swallowing into three stages: during the first, the bolus of food is carried past the anterior pillars of the fauces; during the second, through the pharynx, past the openings of the nasal cavities and of the larynx; and during the third, through the œsophagus into the stomach. There is, however, no pause between these various stages. The act of deglutition is one, and the initiation of the first stage inevitably involves the completion of the whole. The food is masticated, and is collected as a bolus on the dorsum of the tongue. A pause then takes place in the movements of mastication, a slight movement of the diaphragm usually occurs known as 'respiration of

swallowing,' and then a sudden elevation of the tongue throws the bolus back through the anterior pillars of the fauces. In this movement the chief factor is the contraction of the mylohyoid muscle, which presses the tongue against the palate and pushes it backwards. The backward movement of the tongue may also be aided by the contraction of the styloglossus and palatoglossus muscles, which pull the base of the tongue suddenly backwards. These muscles, especially the palatoglossi, serve to close the isthmus faucium, thus preventing any return of the food towards the mouth.

As the food is passing through the upper part of the pharynx, it traverses a region common to the respiratory as well as the digestive passages. Its passage through this region is therefore rapid, and is associated with a closure of the two openings of the air passages into the pharynx. The nasal cavity is shut off by a simultaneous contraction of the levator palati and palato-pharyngeal muscles and azygos uvulæ, by which means the soft

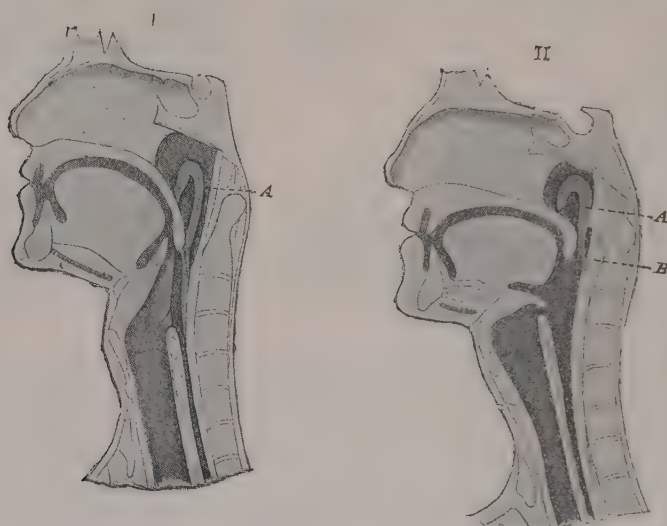


FIG. 303. Diagram to show the Position of the Soft Palate. (After TIGERSTEDT.)
I. During rest. II. During the act of swallowing.

palate is raised (Fig. 303) and the posterior pillars are approximated to the uvula. The upper and back wall of the palate is thus formed into a tense sloping roof which guides the bolus down the pharynx.

More important is the shutting off of the lower air passages. The contraction of the mylohyoid muscles, which initiates deglutition, is followed almost immediately (at an interval of 0.1 sec.) by an elevation of the larynx, and this elevation is accompanied by closure of the glottis as well as of the superior opening of the larynx. The laryngeal opening is bounded in front by the epiglottis, behind by the tips of the arytenoid cartilages, and at the sides, by the aryteno-epiglottidean folds. When deglutition takes place, the arytenoid cartilages, which normally lie against the posterior wall of the pharynx, are rotated and move inwards and forwards, so that the laryngeal opening assumes the form of a tri-radiate fissure, the vertical limb being short, while the transverse limb is rounded owing to the pulling inwards of the margins of the epiglottis. At the same time both the true and false vocal cords come together, while the movement of the dorsum of the tongue backwards enables the closed laryngeal orifice to lie directly under the back

part of the tongue. The muscles which are actively involved in this closure of the lower air passages are the external thyro-arytenoid, arytenoid, ary-epiglottidean, and the lateral crico-arytenoid muscles. Since the approximation of the posterior to the anterior boundary of the laryngeal opening is rendered possible only by the elevation of the whole larynx under

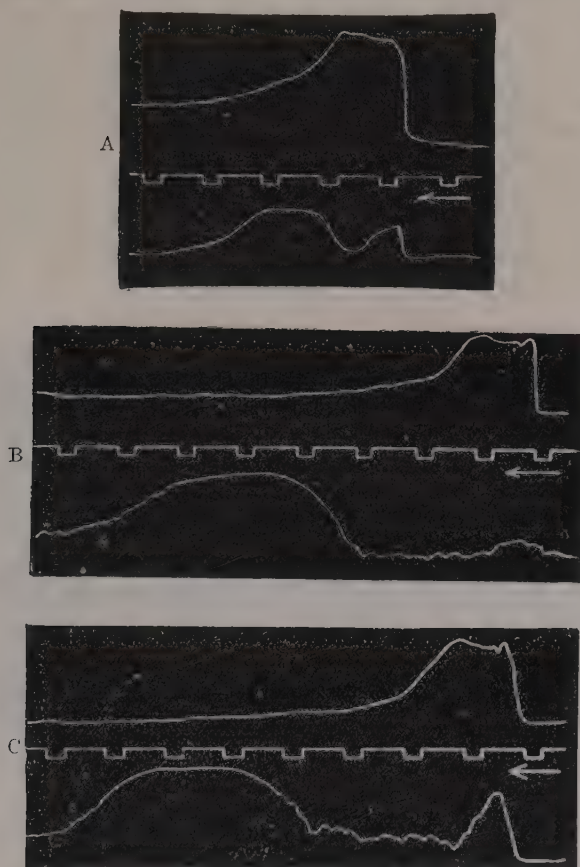


FIG. 304. Curves obtained during Swallowing by Placing Two Rubber Balloons, one (the upper curve) in the Pharynx, the other (lower curve) in the Oesophagus. (KRONECKER and MELTZER.) Read from right to left.

In A the second balloon was 4 cm.; in B 12 cm.; and in C 16 cm. from the upper end of the oesophagus. In each curve it will be noticed that the excursion of the upper lever is followed *immediately* by an excursion of the lower lever (due to passage of the swallowed fluid and transmitted rise of pressure), and then, after an interval of time varying with the distance between the balloons, by another rise due to the peristaltic contraction of the wall of the oesophagus.

the hyoid bone, the act of deglutition cannot be carried out unless the larynx is free to move.

The two openings from the back of the pharynx into the air passages being thus closed, the bolus is shot rapidly past them into the region of the middle and inferior constrictors of the pharynx. If the bolus be liquid or semi-fluid, the movement of the back part of the tongue may be sufficient to propel the substance past the constrictors through the lax oesophagus to its lower end. It is on this account that, when corrosive fluids are swallowed

by accident, we very often find the damage to the œsophagus limited to the three points where it is narrowed and there is a slight hindrance to the onward flow of fluid. If the bolus be large and solid or semi-solid, it is seized in the grasp of the middle constrictors on passing through the upper part of the pharynx, and is thrust by successive contractions of this muscle, and of the inferior constrictor, gradually down the œsophagus (Fig. 304). The walls of the cervical part of the œsophagus are composed of striated muscle. In the thorax, striated and unstriated muscles are associated together, while the lower third, in the neighbourhood of the stomach, consists almost entirely of unstriated muscle. Corresponding to these differences in structure, Kronecker and Meltzer have found differences in the duration and rapidity of propulsion of the contraction waves in each part. The following Table shows the time relations of the chief muscles engaged in deglutition as determined by Kronecker and Meltzer and by Marekwald :

Time from commencement.	Interval.	Muscle movement.	Duration of contraction.
—	—	Mylohyoid	0.6 sec.
—	0.03 sec.	Respiration of swallowing	—
—	0.07 sec.	Elevation of larynx	0.8 sec.
0.3 sec.	0.2 sec.	Constrictors of pharynx	1.0 to 2.0 sec.
—	0.9 sec.	First section of œsophagus	2.0 to 2.5 sec.
3.0 sec.	1.8 sec.	Second section of œsophagus	6.0 to 7.0 sec.
6.0 sec.	3.0 sec.	Third section of œsophagus	about 10 sec.

The free passage of food down the œsophagus under the influence of the propulsive force exercised by the mylohyoid muscles shows that the walls of this tube must be lax, and in fact one must assume that the first act of deglutition, so far as concerns the œsophagus, is an inhibition initiated reflexly with the beginning of the act of deglutition. When a second act of deglutition succeeds the first with a sufficiently short interval, the reflex inhibition due to the second act may prevent the development of any wave of contraction in the œsophagus. This tube thus remains in a lax condition and allows the free rapid passage of the food downwards until the movements of deglutition have come to an end, when a peristaltic contraction occurs and sweeps all remaining adherent particles of food into the stomach. The circular fibres of the lower end of the œsophagus, which form the cardiac sphincter of the stomach, are normally in a state of tonic contraction. When one mouthful of food is swallowed, it may either pass directly into the stomach by gravity, or remain at the lower end of the œsophagus until the following peristaltic wave forces it through the orifice. When several acts of deglutition succeed one another, the cardiac sphincter shares in the inhibition of the œsophageal walls, and offers no resistance to the direct propulsion of food from the mouth to the stomach.

Cannon has shown that the relaxation of the cardiac orifice which accompanies swallowing, extends also to the cardiac end of the stomach. This relaxation lowers the pressure within the stomach, and makes room for the incoming food.

When the contents of the stomach are only feebly acid, the cardiac sphincter opens at intervals, and especially if the pressure in the stomach is high, allowing of the regurgitation of the stomach contents into the lower part of the œsophagus. This is at once followed by a peristaltic contraction of this part of the œsophagus (apparently entirely unconscious), which drives the fluid back into the stomach. It has been supposed that movements of regurgitation become more and more infrequent as the gastric contents become acid; but the modern view associates the increasing tone of the sphincter with distension of the stomach and the stage of digestion.

THE NERVOUS MECHANISM OF DEGLUTITION. Deglutition is a reflex act. Swallowing reflexes are readily elicited in the decerebrate animal, when water or dilute alcohol is placed in the mouth. When we swallow voluntarily we supply the necessary initial stimulus, either by touching the fauces with the tongue, or by forcing saliva or food into the fauces. The afferent channels of the reflex are contained in the second division of the fifth nerve, the glosso-pharyngeal nerve, and the pharyngeal branches of the superior laryngeal

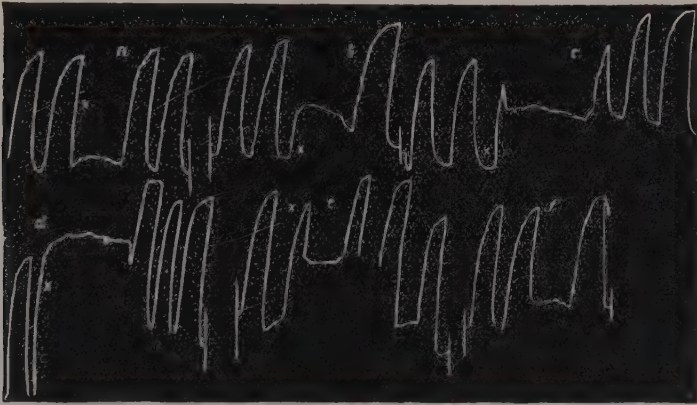


FIG. 305. Tracings of Respiratory Movements to show the Effect of Stimulating the Central End of the Glossopharyngeal Nerve. (MARCKWALD.)

The point of stimulation is marked with a cross. Note that the stoppage may occur at any phase of the respiratory movement.

nerve. We can excite a single act or a whole series of acts of deglutition by electrical stimulation of the central end of the last-named nerve. The efferent fibres travel by the hypoglossal nerve to the muscles of the tongue, by the fifth to the mylohyoid, by the glossopharyngeal, the vagus and the spinal accessory nerves to the muscles of the fauces and pharynx. The closure of the larynx is effected by impulses which travel through the superior and inferior laryngeal branches of the vagus. The centre for the act is situated in the medulla oblongata, and can be considered as consisting of a chain of centres, stimulation of one of which involves the firing off of all the others in orderly sequence; the propulsion of the contraction down the œsophagus is determined by the intracentral nervous connections, and does not require the integrity of the muscular tube itself. If the œsophageal nerves be divided, the act of deglutition is abolished, the upper part of the œsophagus becoming permanently relaxed, while the lower part, including the cardiac sphincter, enters into a state of tonic contraction. On the other hand, the œsophagus may be ligatured or cut across without interfering with the propulsion of the wave of contraction, started in the pharynx, from one end of

the tube to the other. Stimulation applied to the mucous surface of the œsophageal tube is without effect.

There is an important interdependence between the functions of respiration and deglutition. If an inspiratory or expiratory movement were going on during the act of deglutition, food might be drawn into the lungs or driven into the nasal cavities. Such an accident is prevented by the fact that every act of swallowing inhibits a respiratory movement. This inhibition is effected reflexly through the glossopharyngeal nerve. Stimulation of the central end of this nerve at once causes cessation of respiration in whatever phase it may happen to be (Fig. 305). This cessation lasts for five or six seconds, *i.e.* a sufficient length of time for a whole series of acts of deglutition. Respiration then recommences, and the inhibition cannot be prolonged by continuing the stimulation of the glossopharyngeal nerve. This inhibition of the activity of the respiratory centre can be shown on oneself. If the breath be held until the feeling of dyspnœa, *i.e.* the need to breathe, becomes insistent, relief is at once experienced by swallowing, and the feeling of relief will last for three or four seconds.

DIGESTION IN THE STOMACH

GASTRIC JUICE

The stomach consists of a cardiac portion, the corpus or main body, and the pylorus. There are definite differences between these as regards their functions. The normal stomach several hours after food is rarely empty, but usually contains from 30 to 50 c.c. of fluid consisting of gastric juice, mucus, saliva and regurgitated duodenal contents. Within five minutes of the taking of food into the mouth, a secretion of gastric juice begins from the multitude of tubular glands which make up the greater part of the mucous membrane of the stomach. As the food is swallowed in successive portions, it accumulates in a mass in the fundus of the stomach, and the mass thus formed is penetrated with difficulty by the gastric juice, so that salivary digestion can be continued for a considerable time. The flow of juice may continue for several hours and amounts in man, after a good meal, to 500 c.c. or more.

The gastric juice, which is so poured out, can be obtained in various ways. In clinical practice it is used to be the custom to give a definite meal, and then an hour later, to withdraw the contents by a stomach tube, so obtaining a mixture of gastric juice and partially digested food (Ewald). The present method (fractional test meal) consists, after administering a standard meal (*e.g.*, gruel), in withdrawing small samples of the contents at 15 minute intervals through a narrow tube which can be left in place throughout the examination (Rehfuß).

The earliest case in which human gastric secretion was adequately studied by direct observation was a man in whom a permanent gastric fistula remained as the result of a gunshot wound, and who was kept under observation by Beaumont, an American Army surgeon, from 1825-33.

A case has been described by Richet in which, as the result of the accidental taking of a corrosive alkali, the œsophagus had become occluded by cicatrization. In order to preserve the individual from starvation, it was necessary to perform gastrostomy, *i.e.* to make an artificial opening into the stomach through which he could be fed. Although in this patient the passage of anything from mouth to stomach was completely prevented, it was observed that merely taking food into the mouth was followed by the secretion of gastric juice. Pavlov produced this condition artificially in dogs. The œsophagus was divided and the two ends brought to the surface

of the neck. At the same time an opening was made into the stomach. The animals could be fed either through the lower opening of the œsophagus in the neck, or through the gastric fistula. They could also eat and swallow food, but the food thus swallowed fell out of the opening in the neck instead of passing into the stomach. Under these circumstances it is found that the "sham feeding" is quickly followed by a secretion of gastric juice, which can be collected in vessels connected with the fistulous opening. If taken from a fasting animal, such a juice can be regarded as pure gastric juice. It is clear, colourless, strongly acid (pH about 1.0), and without smell. It contains no peptone, but traces of protein. The following table represents its average composition :

Hydrochloric acid	0.46 to 0.58 per cent.
Chlorine	0.49 " 0.62 "
Total solids	0.43 " 0.60 "
Organic solids	— " 0.45 "
Ash	0.09 " 0.16 "
Total nitrogen	0.05 " 0.08 "

Freezing point = $-0.55^{\circ}C$.

If the juice be allowed to stand in the ice chest for a day, it becomes cloudy and deposits a fine floccular precipitate, which contains most of the pepsin, the principal active agent of the juice.

The actions of gastric juice are due partly to the acid, partly to the combined action of the acid and the enzymes. The acid of the gastric juice is entirely hydrochloric acid. Dog's juice contains on the average about 0.6 per cent. HCl; human gastric juice probably contains less, about 0.2 to 0.4 per cent. When, however, we examine the gastric contents, composed of a mixture of gastric juice and semi-digested food, we always find other acids besides the hydrochloric acid, and of these the most prominent is lactic acid. It is produced by processes of bacterial fermentation occurring in the carbohydrates, converting them into sugar and then into lactic acid. As the gastric juice gradually soaks into the food and renders it acid, it stops this lactic acid fermentation.

In some pathological conditions free hydrochloric acid may be entirely wanting from the gastric juice, and the detection of this acid in gastric juice becomes therefore a matter of considerable clinical importance. For this purpose we can employ various indicators, which change colour in the presence of a strong acid such as HCl, but are unaffected by weak acids such as lactic acids or the fatty acids. Chief among these indicators are Congo red, which turns blue with mineral acids, and a slaty colour with lactic acid; and tropæolin 00, which turns a brilliant red in the presence of a free mineral acid, but is unaltered by lactic acid. The reagent which is most employed is Günzberg's reagent. This is a mixture of phloroglucinol and vanillin dissolved in absolute alcohol. A drop of this is evaporated to dryness in a porcelain capsule. A drop of the fluid to be tested is then added, and also evaporated to dryness. If free HCl be present, the residue on drying becomes a brilliant red colour, an effect which is not produced by the presence of free lactic or free fatty acids.

Great stress has been laid on the determination of the actual amount of free H ions present, and for this purpose the acidity of gastric juice or of gastric contents can be measured by the use of suitable indicators, or more directly by the hydrogen electrode. The acidity estimated in this way is diminished considerably by the presence of albumins, and still more by the presence of albumoses or peptones, which act as weak buffers. But it does not seem that the adjuvant action of the acid on the proteolytic powers of the gastric enzyme is in any way affected by the diminution of its acidity caused by the presence of peptone. The coloured indicators mentioned above,

however, serve as trustworthy guides to the amount of free acid present, considered with regard to its digestive functions.

In order to determine quantitatively the amount of free HCl, the following procedure is employed (Mörner and Sjöqvist): Ten cubic centimetres of the gastric juice are neutralised with barium carbonate. The mixture is dried in a platinum dish, incinerated, and the ash extracted with warm water and filtered. In this process the organic salts are destroyed and converted into barium carbonate. The solution therefore contains merely the barium which was taken up to combine with the free HCl. Estimation of the barium in the filtrate gives the amount of BaCl_2 present, and therefore the amount of hydrochloric acid in the gastric juice. The barium is determined by titrating, in presence of sodium acetate and acetic acid, with potassium bichromate solution, 'tetra paper' being used as an indicator. This turns deep blue in the presence of free bichromate in solution.

THE ACTIONS OF GASTRIC JUICE.—By the action of the hydrochloric acid, certain changes are induced in the foodstuffs. Cane sugar is inverted to glucose and fructose; some proteins, such as blood fibrin, are swollen up to form a jelly-like mass. The caseinogen of milk is precipitated, the collagen of the connective tissues is swollen up. It is possible that a small amount of hydrolysis also takes place in the dextrins and maltose produced by the action of ptyalin on starch.

The chief digestive function of the gastric juice is dependent on the action of the enzyme, pepsin. This substance, which is inactive in neutral medium, needs the co-operation of an acid, hydrochloric acid being the most effective, though its place may be taken by phosphoric, sulphuric or lactic acid. Its main effect is on the proteins of the food. The stages in its action may be best studied on blood fibrin. If fibrin be immersed in 0.4 per cent. hydrochloric acid, it swells up to a gelatinous mass. On then stirring in an extract of gastric mucous membrane or any preparation of pepsin, the gelatinous mass rapidly undergoes solution. If the mixture be boiled and neutralised immediately after solution has occurred, nearly the whole of the protein is thrown down in a coagulated form. The first effect therefore is the production of soluble coagulable proteins from the insoluble fibrin. If the action be allowed to proceed for some hours, a whole series of products of hydrolysis is found in the mixture. On neutralising the fluid, a precipitate may be thrown down consisting chiefly of acid meta-protein. The greater proportion of the protein remains in solution. This remainder may be purified from any unaltered coagulable protein by boiling in slightly acid solution and filtering. The filtrate contains a mixture of proteoses and peptones. In the course of peptic digestion it can be shown that COOH groups and NH_2 groups become liberated, and in equal numbers, which shows that pepsin acts by breaking the peptide linkage of proteins.

By means of fractional precipitation with ammonium sulphate or zinc sulphate, these mixtures can be subdivided into various rough groups as shown in the Table on p. 559 (Witte's peptone).

The analysis on p. 560 of the constituents of protoalbumose and hetero-albumose respectively, shows that the different proteoses really correspond to different groupings of the amino-acids making up the original protein molecule.

The results obtained by Pick by hydrolysis of these different bodies show that, in the breakdown of protein by gastric juice, there is a division of the complex molecule into smaller molecules, which are qualitatively different. Thus of the fractions which he obtained, some contain the greater part of the sulphur originally present in the protein molecule, another contains the

Fractions.	Percentage of salt to precipitate.	Albumoses.	Limit of solubility in alcohol.	Composition per cent.				Biuret test.	Millon's test.	Xantho-proteic test.	Indol formed by fusion with KHO	Carbo-hydrate reaction.	Lead sulphide reaction.
				C.	H.	N.	S.						
Hetero- and proto-albumose fraction	$(\text{NH}_4)_2\text{SO}_4$ 24-42	Hetero-albu-mose	Insoluble in 32%	55.12	6.61	17.98	1.22	Present	Very weak	Present	Very weak	Absent	Present
		Proto-albu-mose	Soluble in 80%	55.64	6.80	17.66	1.21	"	Strong	"	Very strong	"	"
Deutero-albumose	$(\text{NH}_4)_2\text{SO}_4$ 54-62 in neutral 47-59 in acid reaction	Thio-albu-mose	Insoluble in 60-70%	48.96	6.90	16.02	2.97	"	Present	"	Present	"	Very strong
		A Albumose poor in sulphur	Soluble in 70%	53.11	7.16	17.86	0.80	"	"	"	"	"	Present
A Fraction	ZnSO_4 54-68 in acid reaction	BI Albu-mose	Insoluble in 35%	—	—	16.94	—	"	"	"	—	"	"
B Fraction	$(\text{NH}_4)_2\text{SO}_4$ 70-95 in neutral 63-77 in acid reaction	BII Albu-mose, Gluco-albumose	Insoluble in 60-70%	48.72	7.03	13.76	30.49	"	"	"	Weak	Very strong	"
		BIII α Albu-mose	Soluble in 80%	43.98	6.41	14.25	1.63	"	"	"	Strong	Absent	Absent
C Fraction	ZnSO_4 68-80 in acid reaction	BIII β Albu-mose	Soluble in 80%	52.32	7.32	15.36	1.21	"	"	"	"	"	"
		Peptomel-anin	Soluble in 80-90%	60.70	6.68	11.46	21.16	Absent	Absent	—	"	"	"
	$(\text{NH}_4)_2\text{SO}_4$ 100 + Acid	C Albumose (Fibrin)	Soluble in 67-80%	34.52 52.68	5.85 6.83	17.24 16.91	42.89 1.10	Present	Faint trace	Very strong	Faint trace	"	"

Peptone A Peptone B	Not precipitated by $(\text{NH}_4)_2\text{SO}_4$ Not precipitated by $(\text{NH}_4)_2\text{SO}_4$	Biuret test.		Millon's test.		Indol formed by fusion with KOH.	Carbohydrate reaction.	Lead sulphide reaction.
		Present	Absent or trace	Absent or trace	Present			
Peptone A	Not precipitated by $(\text{NH}_4)_2\text{SO}_4$	Present	Absent or trace	Absent	Present	Indol formed by fusion with KOH.	Carbohydrate reaction.	Absent
Peptone B	Not precipitated by $(\text{NH}_4)_2\text{SO}_4$	Present	Present	Present	Present	Indol formed by fusion with KOH.	Carbohydrate reaction.	Absent

greater part of the carbohydrate group, while others are free altogether from the tryptophane group which is responsible for Hopkins' reaction obtainable in the original protein.

Proceeding from primary through secondary albumoses to peptones, there is a continuous diminution in the size of the molecule. During the time which gastric juice has to exert its influence, a maximum, say, of twelve hours, the breakdown never passes beyond the albumose and peptone stage, and it is in this form that the proteins of the food pass on into the small intestine.

RESULTS OF THE COMPLETE HYDROLYSIS OF HETERO- AND PROTOALBUMOSE

	Heteroalbumose.	Protoalbumose.
Glutaminic acid	9.51	0.63
Leucine	3.05	5.79
Isoleucine	2.96	1.62
Valine	3.54	0.76
Alanine	3.39	2.50
Valine-alanine mixture	1.86	0.00
Proline	4.27	4.96
Phenylalanine	2.45	4.35
Aspartic acid	4.73	2.98
Glycine	0.15	1.44
Tyrosine	3.48	4.58
Arginine	7.30	7.72
Histidine	3.90	2.77
Lysine	8.90	8.40
Cystine	1.36	0.68
Ammonia	1.28	0.92

ACTION ON OTHER PROTEINS. *Collagen.* The connective tissues are made up chiefly of collagen. This substance forms the main basis of areolar tissue, of white fibrous tissue and of bone. On prolonged boiling it is converted into gelatin. The gastric juice dissolves collagen, converting it, probably through the stage of gelatin, into gelatoses and gelatin peptones, bearing the same relation to the original substance as is borne by the proteoses and peptones to the proteins. On account of this action, adipose tissue (which consists of protoplasmic cells distended with fat and bound together by connective tissue) is broken up into its constituent cells. The protoplasmic pellicle is dissolved, and the fat floats freely in the gastric juice.

Elastin, which also occurs in varying amounts as the chief constituent of the elastic fibres of connective tissues, is only very slowly acted upon by gastric juice. In natural gastric digestion it may be regarded as indigestible.

Mucin, which forms a considerable proportion of the ground substance of connective tissues, is converted by gastric juice into peptone-like substances, and into reducing bodies allied to glucosamine.

The *Nucleo-proteins*, the chief constituents of nuclei, are first dissolved by the acid of the gastric juice, and are then broken up into two moieties. The protein half is converted into proteoses and peptones, while the nuclein moiety is precipitated in an insoluble form.

On *Phospho-proteins* gastric juice acts in a somewhat similar manner. but caseinogen undergoes special changes in the stomach. The first effect of gastric juice, even in neutral medium, is to convert the caseinogen into an insoluble casein. This action is often ascribed to the presence of a distinct enzyme of the gastric juice, named *rennin*. But, according to some authorities, it is due directly to the pepsin, *i.e.* *rennin* and pepsin

are identical. For the conversion of caseinogen into the solid clot of casein the presence of lime salts is necessary. The addition of rennet to an oxalated milk apparently produces no effect, but clotting ensues if a soluble lime salt, such as calcium chloride, is then added to the mixture. It is therefore thought that, in the clotting of milk, the caseinogen under the action of the rennet first undergoes a conversion into a soluble casein, or perhaps a splitting into a soluble casein and some other substance. The soluble casein then, under the influence of the lime salts, forms an insoluble casein, which is precipitated and causes the solidification of the milk. In the absence of lime salts, the conversion or splitting of caseinogen takes place, but the second stage of the process cannot occur until the lime salts are added. Under the further action of the acid gastric juice, the clot of casein first formed is dissolved, but a precipitate is left containing a small proportion of the original phosphorus of the caseinogen. This precipitate is sometimes spoken of as *para-nuclein*, or *pseudo-nuclein*. It does not yield purine bases on hydrolysis with acids, but contains phosphoric acid in organic combination. By prolonged digestion with strong gastric juice it is possible to dissolve the whole of this precipitate.

ACTION ON CARBOHYDRATES. It seems probable that the inversion, *i.e.* the hydrolysis, of cane sugar which takes place in the stomach can be completely accounted for by the action of hydrochloric acid present, and that there is no need to assume the presence of a special enzyme.

In the same way inulin, which gives rise to the *lævorotatory* sugar, fructose, on hydrolysis, is converted by the acid of gastric juice into fructose. The inulin is therefore completely utilised in the alimentary canal of animals. although there is no definite enzyme *inulase* provided for its hydrolysis.

ACTION ON FATS. The chief action of this juice on fats is the solution of their connective tissue framework and protoplasmic envelopes, so as to set the fat free in the gastric contents. After a fatty meal it is found moreover that a considerable proportion of the fat in the stomach has undergone hydrolysis and conversion into free fatty acid. In this hydrolysis three factors are involved: (1) the action of the warm dilute hydrochloric acid; (2) the action of a *lipase*, which is secreted by the walls of the stomach, and acts especially at the beginning of gastric digestion before the contents have attained a high degree of acidity. The action of this enzyme is conspicuous only if the fat be present in a finely divided form, as in yolk of egg; (3) the action of lipase regurgitated from the duodenum. The chief digestion of fat takes place in the duodenum.

THE SECRETION OF GASTRIC JUICE

Histological investigations show that four types of cells are recognisable in the gastric mucosa, *viz.* surface, mucoid, peptic and oxyntic cells (Lim). The surface cells cover the inner surface of the mucosa, and line the ducts of the tubular gastric glands; they secrete mucus. Mucoid cells form the secreting cells of those pyloric and cardiac glands which are placed near the two sphincters; they are also mingled with the peptic cells lining the cardiac glands. They are probably closely connected in function with the peptic cells, since in new-born animals they precede these in the cardiac glands. The peptic or chief cells secrete pepsin, and the oxyntic or parietal cells the hydrochloric acid. The cytoplasm of the latter reacts acid during active secretion.

The normal resting stomach secretes some gastric juice; the juice which is formed by it appears to consist of a mucilaginous secretion, rich in pepsin, but containing little or no acid,

In the 'sham feeding' experiment carried out as already described, secretion of gastric juice rich in acid begins in about five minutes after the onset of feeding, and continues as long as this goes on, which may be for several hours. This method does not, however, enable us to determine whether the character of the juice will be altered in any way by the changes which the food undergoes in the stomach itself. In order to form an idea of the normal course of secretion of gastric juice when food is taken into the stomach in the ordinary way, Pavlov has devised another procedure. A small diverticulum, representing about one-tenth to one-fifth of the whole stomach, is made, usually in the body of the stomach, in direct muscular and nervous continuity with the rest of the stomach, but shut off from the main part of the viscus by a double diaphragm of mucous membrane. The outline of this rather complicated operation is indicated in the diagram (Fig. 306). In a dog treated in this way it is found

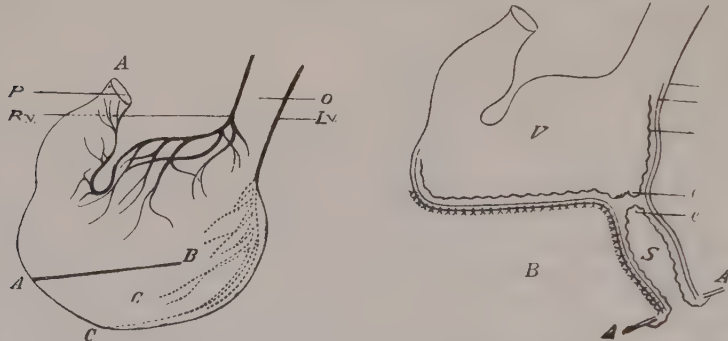


FIG. 306. Diagram to show Pavlov's Method of making a Cul-de-sac of the Body of the Stomach, with Vascular and Nerve Supply intact.

In A the line of the incision into the gastric wall is shown. B represents the operation as completed.

In A: *O*, oesophagus; *R.v.*, *L.v.*, right and left vagus nerves; *P*, pylorus; *C*, corpus, or body of stomach; *A.B.* line of incision.

In B: *V*, main portion of stomach; *S*, the cul-de-sac; *A*, abdominal wall; *e, e*, mucous membrane reflected to form diaphragm between the two cavities.

that the amount of juice secreted by the small stomach bears always the same ratio to the amount secreted by the large stomach, while the digestive power of the juice obtained from the small stomach is equal to that obtained from the large. This is shown in the following Table, from an experiment in which there was also a fistula into the main stomach, and in which secretion was excited by sham feeding :

SECRETION FROM GASTRIC FISTULÆ AFTER SHAM MEAL

Hours.	Small stomach.		Large stomach.	
	Quantity.	Strength.*	Quantity.	Strength.
1	7.6 c.c.	5.88 mm.	68.25 c.c.	5.5 mm.
2	4.7 c.c.	5.75 mm.	41.5 c.c.	5.5 mm.
3	1.1 c.c.	5.5 mm.	14.0 c.c.	5.38 mm.
Total . .	13.4 c.c.	—	123.75 c.c.	—

* The strength of the juice was determined by measuring the number of millimetres of coagulated egg-white (in Mett's tubes) which were digested in eight hours.

We may therefore regard the secretion obtained from the small stomach as a sample of that produced by the large, and from the changes in this small stomach either study the effects of a normal meal in which the food is swallowed, or of a sham meal in which the food is merely masticated in the mouth, or of a meal in which the food is directly introduced into an opening into the large stomach.

The fact that sham feeding suffices for the collection of gastric juice shows that we have to do, in the first place, with a reflex nervous mechanism. This is an unconditioned reflex. But a secretion, which is at least as vigorous as that produced by a sham meal, can be evoked through a conditioned reflex, by merely providing some stimulus associated with the animal's food habits. If the animal be hungry, it is sufficient to show it the food to produce this effect. In the experiment from which the following Table is taken, the dog was continually excited by showing it meat during a period of an hour and a half. At the end of this time the animal, which had an œsophageal fistula, was given a sham meal. It will be observed that the 'psychical secretion' obtained during the first period of the experiment was rather greater than the secretion produced by the introduction of food into the mouth.

PSYCHICAL SECRETION OF GASTRIC JUICE (PAVLOV)

Time.	Quantity.
8 minutes	10 c.c.
4 "	10 "
4 "	10 "
10 "	10 "
10 "	10 "
8 "	10 "
8 "	10 "
19 "	10 "
9 "	3 "

SHAM FEEDING

Time.	Quantity.
17 minutes	10 c.c.
9 "	10 "
8 "	10 "

The afferent channels for this reflex may therefore be either the afferent nerves from the mouth or, in the conditioned reflex, any of the nerves of special sense, such as sight, smell or hearing, which have, by being brought into use in association with the unconditioned reflex, acquired the properties of conditioned afferents.

The efferent channels can be only one of two nerves, the vagus and the sympathetic, since these are the only two which are distributed to the stomach. That the former of these nerves is involved is shown by the fact, recorded by Pavlov, that psychical secretion, as well as the results of a sham meal, is entirely abolished by division of both vagi.

The converse experiment of exciting secretion by direct stimulation of the vagus has been carried out by Pavlov as follows: An animal with fistulæ of œsophagus and stomach had one vagus nerve divided in the neck. A thread was attached to the peripheral end of the cut vagus and allowed to hang out through the wound. Four days after the operation, the vagus was drawn out of the wound by carefully pulling on the thread, so as not to hurt or frighten the animal in any way, and its peripheral end stimulated by means of induction shocks. No effect was produced on the heart, owing to the degeneration of the cardio-inhibitory fibres, which is well known to occur within this period after section. Five minutes after the commencement of the stimulation the first drop of gastric juice appeared from the gastric cannula, and a steady secretion of

juice was obtained with continuation of the stimulation. There is one marked difference, however, between the action of the vagi and the action of the chorda tympani nerve on the submaxillary gland; namely, the great length of the latent period before gastric secretion begins. This has not yet been satisfactorily explained. It cannot be due to delay occurring between the vagus fibres and the local nervous mechanism in the stomach. Physiologically there is indeed no special need for a rapid secretion of gastric juice, whereas in the mouth it is essential that the introduction of food should be immediately followed by the production of saliva, for the tasting and testing of the food and for its subsequent mastication or rejection.

The vagus also contains secretory inhibitory fibres, which have the effect of stopping or diminishing the secretion under certain conditions. The sympathetic supply is vaso-constrictor, but stimulation of the splanchnic nerves five days after section (to allow degeneration of vaso-constrictors) gives a secretion of gastric juice, as also, according to most observers, does the injection of adrenaline. In emotional states the secretion of gastric juice is greatly reduced.

These experiments show conclusively that an important—probably the most important—part of the gastric secretion is determined by a nervous mechanism. This nervous secretion does not, however, account for the whole of the gastric juice obtained as the result of a meal, since further secretion is effected in consequence of the presence of certain substances in the stomach itself and also in the duodenum. If an animal provided with two gastric fistulæ, one into a diverticulum and the other into the main stomach, has both its vagi divided, it is found that the introduction of meat into the large stomach is followed, after a period of twenty to forty-five minutes, by the secretion of gastric juice from the small stomach. Moreover, when an animal is given a normal meal and is allowed to swallow the food after mastication, the total amount of gastric juice obtained is greater, and the flow is of longer duration, than that produced by the sham feeding alone. This combined character of the gastric juice produced by a normal meal is shown in the following table (Pavlov):

SECRETION OF GASTRIC JUICE

Hours.	Normal meal. 200 grm. meat into stomach.		150 grm. meat direct into stomach.		Sham meal.		Sum of two last ex- periments.
	Quantity c.c.	Strength mm.	Quantity c.c.	Strength mm.	Quantity c.c.	Strength mm.	Quantity c.c.
1	12.4	5.43	5.0	2.5	7.7	6.4	12.7
2	13.5	3.63	7.8	2.75	4.5	5.3	12.3
3	7.5	3.5	6.4	3.75	0.6	5.75	7.0
4	4.2	3.12	5.0	3.75	0	0	5.0

In the first section is given the result of a normal meal on the secretion from the gastric diverticulum. In the second section are given the amount and digestive power of the juice which is excited by the direct introduction of 150 grammes of meat into the large stomach of the animal, care being taken not to excite the reflex mechanism. In the third section are given the amount and digestive power of the juice which is evoked by a sham meal of 200 grammes of meat. In the fourth section is given the sum of the last two experiments. It will be seen that the total effect of the sham meal *plus* the direct introduction of meat into the stomach is almost identical with the secretion obtained when the food is taken in a normal way.

We may say that the gastric secretion in response to a normal meal shows

three phases: (1) a *reflex phase*, which begins within five minutes of the taking of the food and is determined by the reflex nervous mechanism described above; and (2) a smaller portion, the *second phase*, the secretion of which is excited by the presence of the food in the stomach; (3) the *third phase*, small and variable, and due to the presence of food in the duodenum.

The second phase of the gastric secretion cannot be ascribed to the intervention of any reflex, since it occurs after cutting off the stomach from its connections with the central nervous system. Ivy and Farrell have transplanted a denervated miniature stomach into the mammary region, and found that the second phase still occurred in it about three to four hours after the animal was fed. Its cause must be something carried by the blood. It cannot be due to mechanical stimulation, since the pouch is empty. Moreover it is not produced by all sorts of food. The introduction of white of egg, of starch or of bread into the stomach causes no secretion. On the other hand, if bread and gastric juice be allowed to digest for some time, the introduction of the mixture into the stomach evokes a secretion. So also will glucose, lactic acid, sodium bicarbonate, soap, saliva, or meat; still more potent than meat, however, is a decoction of meat, or bouillon, or Liebig's extract of meat, or peptone or albumoses. The exciting mechanism must be some chemical substances present in meat, and produced in various other foods under the action of the first gastric juice secreted in response to nervous stimuli. Certain substances, *e.g.* histamine, are known to produce gastric secretion when injected into the blood stream. Although the peptogenic substances which evoke gastric secretion on introduction into the stomach have little or no effect on the gastric glands when injected directly into the blood stream, it is possible that they may have an influence on the cells which line the cavity of the stomach, and that they may produce, in these cells, some other substance which is absorbed into the blood and acts as a specific excitant of the gastric glands. A process of this nature is known to occur in the duodenum, where it determines the secretion of the pancreatic juice and the bile.

Edkins carried out a series of experiments which indicate that such a chemical mechanism may also account for the second phase of the secretion of gastric juice. Edkins' experiments were carried out in the following way: The animal, dog or cat, having been anæsthetised, the abdominal cavity was opened, and a ligature passed round the lower end of the œsophagus so as to occlude the cardiac orifice and effectually crush the two vagus nerves. A glass tube was then tied into the pyloric part of the stomach, and connected by means of a rubber tube with a reservoir containing normal salt solution at the temperature of the body. By means of this reservoir, a certain amount of fluid was introduced into the stomach and kept there at a constant pressure; the quantity of fluid introduced varied from 30 to 50 c.c. Since no absorption of water or saline fluid occurs in the stomach, it is possible to recover the whole of the fluid an hour after it has been introduced. If secretion of gastric juice has occurred into the cavity of the stomach, the fluid will be increased in amount and will contain hydrochloric acid as well as pepsin. Control observations showed that the mere introduction of this fluid into the stomach caused no secretion of gastric juice. Edkins then showed that the injection of peptone, of acid, of broth or of dextrin into the blood stream also produced no secretion of gastric juice. If, however, in the course of the hour during which the fluid was allowed to remain in the stomach, a decoction made by boiling pyloric mucous membrane with acid, with water or with peptones, was introduced in small quantities every ten minutes into the jugular vein, the

fluid removed at the end of the hour was found to be distinctly acid in its reaction and to possess proteolytic properties. The injection of these substances had therefore caused the secretion of a certain amount of gastric juice. In order to produce this positive effect, it was necessary to employ pyloric mucous membrane, extracts from fundic mucous membrane being without effect. Edkins concluded therefore that the secondary secretion of gastric juice is determined by a chemical mechanism. The first products of digestion act on the pyloric mucous membrane, and produce in or extract from this membrane a substance which is absorbed into the blood stream, and carried to all the glands of the stomach, where it acts as a specific excitant of their secretory activity. This substance may be called *gastrin* or the *gastric hormone*.

After resection of the pyloric part of the stomach this second phase is absent (Smidt). The chemical theory of the second phase of gastric secretion has been fully confirmed by Savitsch and others. Savitsch carried out the surgical operation of isolating the pylorus from corpus and duodenum, dividing all its nerves, and making fistulæ into this isolated pylorus and into the body. Introduction of chemical excitants into the pylorus evoked gastric secretion in the body.

It is an apparent anomaly that the action of the chemical excitants of gastric secretion is inhibited by atropine.

The normal gastric secretion is therefore mainly due to the co-operation of two factors. The first and most important is the reflex secretion, determined through the vagus nerves by stimulation of the mucous membrane of the mouth, or by conditioned reflexes involving the higher parts of the brain. The second factor, which provides for the continued secretion of gastric juice long after the reflex effects of feeding have disappeared, depends on the production in the pyloric mucous membrane of a specific substance or hormone, which acts as a chemical messenger to all parts of the stomach, being absorbed into the blood and thence exciting the activity of the various secreting cells in the gastric glands.

Pavlov has shown that the second phase of the gastric secretion is largely influenced by the character of the contents of the stomach. Thus the ingestion of large quantities of oil considerably diminishes the amount of gastric juice secreted, as well as the acid and pepsin content, and Pavlov has suggested the administration of oil or oily foods as a possible remedy in cases where the production of gastric juice, and therefore of hydrochloric acid, is in excess.

The third, or intestinal phase of gastric secretion, is similarly due to the formation, in the duodenum or upper part of the small intestine, of a gastric hormone which enters the circulating blood. It is relatively much smaller in amount than the second phase, and is demonstrated on dogs with gastric and duodenal fistulæ and with the stomach closed off from the duodenum, or else by uniting the œsophagus with the duodenum so as to isolate the stomach altogether (Ivy, Lim and McCarthy). Gastric secretion results when many substances are introduced into the duodenum, *e.g.* water, meat, meat extract, peptones and other products of protein digestion, &c., while *inhibition* of secretion is said to occur when sodium bicarbonate is introduced. With the sole exception of dilute alcohol, introduction of no substance into the large intestine produces any secretion.

As sodium bicarbonate is so often administered to patients, its effects on gastric secretion may be noted. Taken on an empty stomach it passes direct to the duodenum and inhibits gastric secretion. Taken with or after food it increases secretion by its effect on the pyloric mucosa.

A further important question has been propounded by Pavlov, as to whether there is any alteration in the constitution and amount of gastric juice with variations in the character of the food. So far as concerns the first phase of secretion, the 'appetite' juice, this observer has shown that, whatever the previous diet of the animal, the

juice always has the same characters, the same digestive power and the same percentage of hydrochloric acid. He finds, however, that in the case of the second, or 'chemical' secretion, there is considerable variation in the nature of the juice. Whereas the secretion of juice is greatest in amount after a meal of meat, the digestive power of the juice is greatest after one of bread. We have seen that the psychical juice depends merely on appetite, and therefore will be greater in amount the more welcome the food is to the animal. On the other hand, the juice secreted in the second phase must vary according to the quantity of gastric hormone produced in the pyloric mucous membrane, and therefore with the nature and amount of the substances produced in the preliminary digestion of the gastric contents by means of the psychic juice. The amount of juice may vary also with the salts contained in the food, according to their alkaline or acid character; and the percentage of pepsin in the juice may vary with the intensity of stimulus as well as with the quantity of fluid available for the formation of the gastric juice. Fats reduce the gastric secretion and prolong the stay in the stomach.

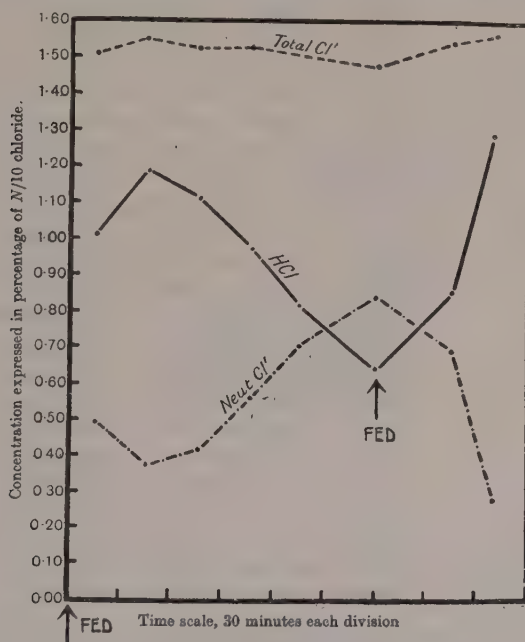


FIG. 307. Curves of Acid, Neutral Chloride and Total Cl of juice from an Isolated Gastric Pouch in a Dog fed twice on meat, once at the beginning and once three hours later. (MACLEAN, GRIFFITHS and WILLIAMS.)

Water, tea or coffee taken with food augment gastric secretion, and various articles of food, such as vegetable juices, contain powerful chemical excitants. Again, slight distension of the pylorus, though not capable of producing secretion, exerts an augmenting effect when gastric secretion is in progress. These factors will co-operate in determining the characters of the whole juice secreted after any given meal.

A further question of considerable importance is that of the acidity of the gastric contents. The optimum acidity is about 0.2 per cent. HCl, and although pure gastric juice secreted at the commencement of a meal contains about 0.5 per cent. HCl, the whole contents rarely, if ever, reach so high a level. This has been explained as being due to neutralisation of excess of acid by the regurgitation of duodenal contents, but MacLean and Griffiths believe this explanation to be inadequate. They claim that, both in man and in dogs with miniature stomachs, where regurgitation is excluded, the acid first rises and then falls. But when the *total chlorine ion* of the contents was estimated it was found to remain constant. They believe, therefore, that the chlorine ions are secreted at a constant concentration, *either* as acid or as neutral chloride. At first the acid preponderates, but afterwards this falls, so that the acidity is reduced by dilution of the contents with a less acid juice richer in neutral chlorides (Fig. 307).

THE MOVEMENTS OF THE STOMACH

These can be best studied by direct observation of the movements in a living unanæsthetised animal or man by means of the X-rays. In order to

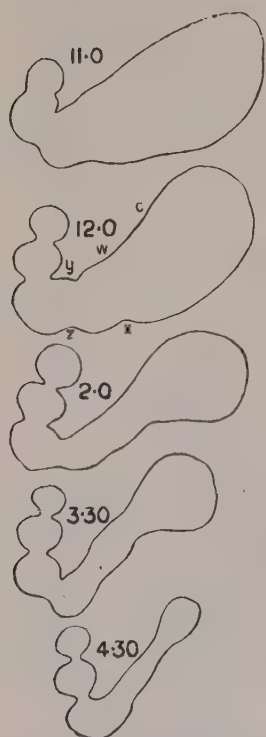


FIG. 308. Shadow Sketches of the Outlines of the Stomach of a Cat, immediately after a Meal (11.0), at various intervals afterwards (12.0, 2.0, 3.30, 4.30). (W. B. CANNON.)

c. Situation of œsophageal opening.

yz. 'Transverse band.'

wx. Junction of body and pyloric portions.

make the shape of the stomach visible, the food—bread and milk—is mixed with a quantity of barium sulphate or bismuth oxychloride (Hurst). The presence of these does not interfere with the processes of digestion, but renders the gastric contents opaque to the Röntgen rays. On examining by this means the stomach of a cat which has just taken a meal, the whole of the food is seen to be lying in the corpus, or body of the stomach, (often called the fundus in animals), which is marked off by a strong constriction, the 'transverse band,' from the pyloric portion. After a while, faint waves of contraction, originating at the cardiac end, travel slowly towards the pylorus, gaining in power as they go. These waves succeed one another, so that the pyloric part of the stomach may present a series of constrictions. Their effect is to force towards the pylorus the food which has been digested by gastric juice and detached from the surface of the mass in the corpus. The pylorus remaining closed, the food cannot escape, and therefore is squeezed back, forming an axial reflux stream towards the cardiac end. These contractions last throughout the whole period of gastric digestion, and become more marked as digestion proceeds. By their action the whole of the food is brought in close contact with every particle of pyloric mucous membrane and a thorough mixture of food and gastric juice results. At varying periods after a meal, according to the nature of the food taken, the arrival of one of these waves of contraction at the pylorus is followed by a transitory relaxation of the orifice, and a few cubic centimetres of gastric contents are squirted into the first part of the duodenum. While these movements of the 'pyloric mill' are going on, the body of the stomach is exercising a steady pressure on its contents, in consequence of a tonic contraction of its muscular wall, so that each successive portion of the food mass which is loosened by the digestive action of the gastric juice is forced on into the pyloric mill. As digestion proceeds, the opening of the pylorus becomes more frequent. The stomach empties itself more and more, until finally the whole of the viscus has the shape of a curved tube (Fig. 308). At the very end of digestion the pylorus may open to allow the passage even of undigested morsels of food.

Very similar are the changes in the human stomach. The term *fundus* is limited to that part of the stomach situated above the cardiac orifice (in the erect position). The *body* of the stomach is marked off, more or less, by the *incisura angularis* on the lesser curvature, corresponding to what we have called the transverse band. The pyloric portion consists of the *pyloric antrum*

and the *pyloric canal*, the latter being a tubular portion about 3.0 cm. in length, especially well marked in infants. When food has been swallowed (in the erect position) its weight is sufficient to overcome the resistance of the contracted gastric wall, and some of it rapidly passes to the pyloric part. Peristalsis begins almost at once, each constriction starting near the middle of the stomach, and deepening as it slowly progresses towards the pylorus (Fig. 309). The wave as it travels along exhibits every two to three seconds the rhythmic fluctuations in intensity common to most plain muscle contractions, and when a wave at a phase of increase reaches a point about one inch from the pyloric canal it is so marked that part of the pyloric antrum becomes almost completely separated from the rest of the stomach. The part thus cut off then diminishes in size in every direction, part of its contents being forced through the pyloric canal, while the remainder escapes

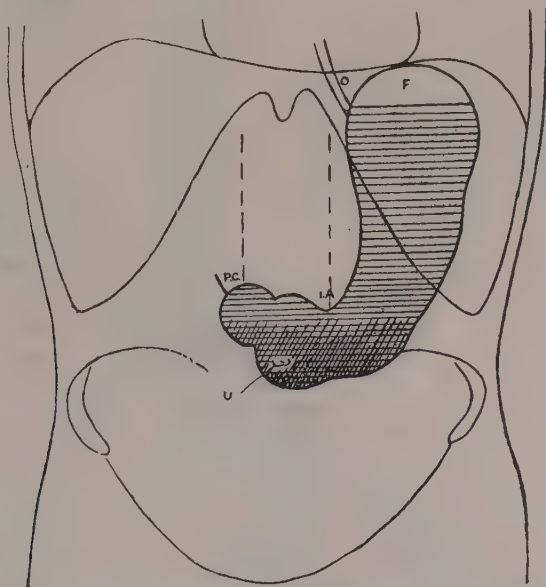


FIG. 309. Sketch of Human Stomach, in Erect Position, shortly after a Bismuth Meal. (HURST.)

F. Fundus. U. Umbilicus. IA. Incisura angularis.
PC. Pyloric canal. O. Œsophagus.

back as an axial reflux stream into the stomach. The waves recur at regular intervals of fifteen to twenty seconds, and three or four are present simultaneously. They continue without cessation until the stomach is empty—from one to four hours after the meal, according to its bulk and composition.

If warm fluid alone, *e.g.* water, be swallowed, the opening of the pylorus occurs within a very short time after the fluid has reached the stomach. Thus if a large draught of water be taken to quench thirst, it may arrive in the duodenum within a minute or two after being swallowed, and it is from the duodenum and small intestine that any absorption takes place.

When a meal is undergoing digestion, there is a distinct, though possibly fortuitous, relation between the amount of acid present in the gastric contents and the opening of the pylorus. It has indeed been thought that the acidity of the gastric contents exercises a direct inhibitory action on the pyloric sphincter, but recent work has shown that this is not the case. It appears more likely that the onward passage of gastric contents

depends on two factors, first, the relaxation of the pyloric sphincter, and second, the relative pressures in the pyloric antrum and the first part of the duodenum (duodenal cap). When a wave in an intense phase reaches the pyloric antrum, the sphincter relaxes before it, and as the pressure in the antrum is high, its contents escape into the duodenum. The contraction wave then involves the sphincter and closes it.

Meals of different foodstuffs remain in the stomach for different periods.

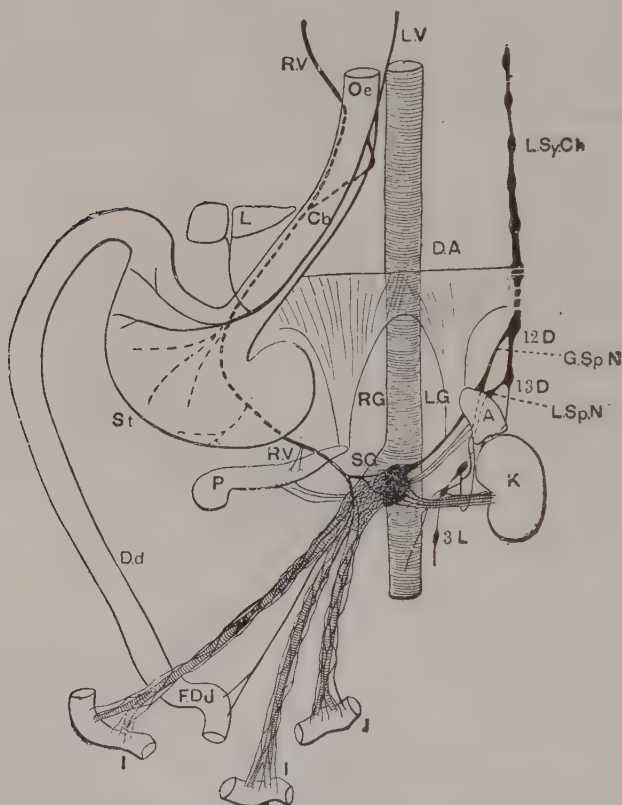


FIG. 310. Distribution of the Vagus in the Abdomen of the Dog.
(M. H. NAYLOR.)

RV, LV, right and left vagi. The right vagus runs behind the oesophagus (Oe) and stomach (St), and in those places is represented by a discontinuous line. Cb, connecting branch between right and left vagi; P, pancreas; Dd, duodenum; FDJ, flexura duodeno-jejunalis; I, I, I, intestine; L, liver; K, kidney; A, suprarenal capsule; RG, LG, right and left cura of diaphragm; L.Sy.Ch, left sympathetic chain; 12 D, 13 D, twelfth and thirteenth dorsal ganglia; 3 L, third lumbar ganglion; G.Sp.N, L.Sp.N, great and small splanchnic nerves; S.G. left semilunar and superior mesenteric ganglia; D.A. dorsal aorta.

Carbohydrates leave early, whereas in presence of fats there is longer retention. Towards the end of digestion the pyloric sphincter begins to relax even when there is no strong wave passing the antrum, and then a regurgitation of duodenal contents into the stomach will occur if the pressure is higher in the duodenum than in the antrum. The normal pressure in the duodenum is about 15 cm. water, and the pyloric intragastric pressure only 10 cm. during relaxation, but 20 to 30 cm. during an intense wave.

The contractions of the duodenum itself play an important part in regu-

lating the emptying of, and regurgitation into, the stomach. Forward contractions empty the duodenal cap and facilitate exit from the stomach. Antiperistalsis also occurs and, by filling the duodenal cap, gives an opportunity for regurgitation (Bolton).

Movements of the stomach may be observed even on a stomach which has been excised and placed in warm salt solution. They must therefore have their origin in the walls of the stomach itself. Although the co-ordination between the two parts of the stomach, between the tonic contractions of the fundus and the rhythmic contractions of the pyloric part, may be carried out by the local nervous system—Auerbach's plexus—situated between the layers of the muscular coat, it is probable that the advancing waves of contraction observed in the antrum are myogenic, *i.e.* directly originated in and determined by the muscle fibres themselves. Cannon has shown that these movements persist after complete division of Auerbach's plexus by from two to six circular incisions carried through the muscular coat of the stomach. The opening of the pylorus on the other hand, which occurs at increasingly frequent intervals at the end of a wave, must be ascribed to a nervous mechanism. Although the local mechanism probably plays the greater part in this act of relaxation, the normal emptying of the stomach is also largely dependent on the integrity of the connection of this viscus with the central nervous system. If both vagus nerves be divided in a dog below the point at which they give off their branches to the lungs and heart, a large amount of food may remain in the stomach in an undigested condition. The secretion of gastric juice is deficient, and the opening of the pylorus is not easily carried out.

When the stomach is empty the pylorus is often relaxed, admitting of the free entry of duodenal contents (pancreatic juice and bile) into the stomach. But this regurgitation, especially of pancreatic juice, seems to be a frequent phenomenon even during digestion, and to be a means by which the acidity of the gastric contents is prevented from rising above an optimum of 0.15 to 0.2 per cent. HCl.

Fractional examination of the gastric contents shows that, normally, the acidity reaches a maximum and then declines; after the decline has begun, bile is present in the fractions, showing that regurgitation has occurred (Fig. 311). If regurgitation is prevented in any way, the contents do not show the declining acidity, and no bile is found (Bolton).

The exact parts played in this mechanism by the local system and by the central nervous system respectively have not yet been thoroughly made out, though there is no doubt that these movements may proceed independently of any connection with the central nervous system.

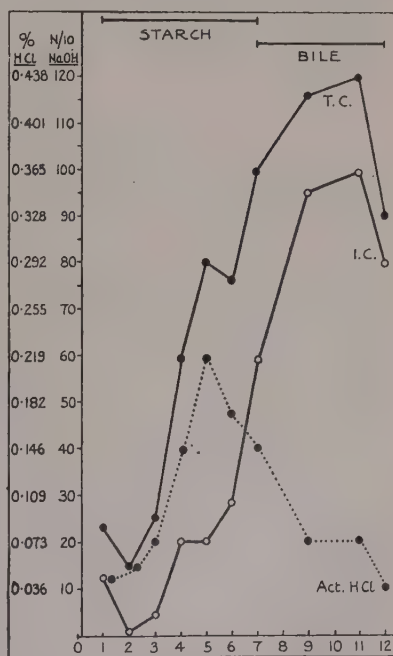


FIG. 311. Analysis of Gastric Contents at 15 min. intervals after a Test Meal of Gruel. T.C., total chlorides; I.C., inorganic chlorides. Act.HCl, 'active' hydrochloric acid. (BOLTON.)

The 'acid control of the pylorus' is certainly not the only factor at work. It has been shown by Campbell that in certain cases, otherwise normal, there may be complete achlorhydria, *i.e.* absence of free HCl from the gastric juice; and yet the movements and emptying of the stomach may present nothing abnormal. Liquids leave the stomach earlier than solid material, and it is known that, whereas distension of the duodenum delays emptying, distension of the stomach promotes it. The work of Apperly suggests that the chief factor is the osmotic pressure of the gastric contents; the nearer this approaches to that of the saline constituents of the plasma, the more readily does the pyloric sphincter open; the duodenum only accepts chyme possessing approximately this osmotic pressure, otherwise regurgitating it back into the stomach.

Stimulation of the peripheral end of the vagus nerves may exercise varying effects on the gastric wall as well as on its sphincters. In the normal animal, stimulation of the peripheral end of the vagus as a rule causes strong contractions of the oesophagus as well as of the cardiac sphincter. After the administration of atropine, stimulation of the same nerve will occasion dilatation of the cardiac sphincter. On both cardiac and pyloric portions of the stomach the vagus exercises inhibitory as well as augmentor effects. So far as concerns the musculature of the fundus or body of the stomach, the most usual result is an inhibition during stimulation of the vagus, succeeded by an augmented tonus immediately the stimulus is removed. If the vagus be excited a number of times, the tonus of the muscular wall augments with each stimulus. On the pyloric portion, stimulation of the vagus also causes inhibition, followed by contraction and augmented peristaltic waves. McSwiney and Wadge find that the effect of vagus stimulation on the stomach as a whole depends on its state of tonus. When the tonus is low, stimulation of the vagus causes contraction; when it is high, relaxation results. In the pylorus itself we may obtain from vagal stimulation either increased or diminished contraction. Whether the splanchnic nerve has a direct influence on the movements of the stomach has been disputed. Most observers regard the splanchnic as having an influence on the stomach similar to its action on the intestine, and regard it as the chief inhibitory nerve to this organ. According to Page May, the blood vessels being constricted, an artificial anæmia is produced, which in itself is sufficient to account for diminished activity.

Carlson has shown that the 'pangs of hunger' are associated with, and are probably due to, prolonged rhythmic contractions of the stomach wall, which come on as soon as the stomach is empty, and increase in force and frequency; each contraction lasts about 20 seconds, and is accompanied by salivation and augmentation of the knee-jerks. The hunger contractions are inhibited by the introduction of food into the stomach, and also by the act of swallowing.

VOMITING

Expulsion of the stomach contents may occur as a result of over-distension of this organ, especially of the pylorus, of the presence of irritating material in its contents, or from abnormal conditions of the brain. It is generally preceded by a feeling of nausea, associated with excessive salivation. The large quantities of saliva swallowed still further distend the stomach and assist the opening of the cardiac orifice. In the act of vomiting itself, the first event is a deep inspiration. The glottis is then closed, and this is followed by a strong contraction of the diaphragm and of the abdominal muscles. At the same time the cardiac orifice is actively relaxed. By means of X-rays it is seen that at this time a strong contraction occurs at the incisura angularis, dividing the stomach into two separate portions. The dilated body of the stomach is pressed between the abdominal muscles and the diaphragm, so that its contents are expelled through the relaxed oesophagus and out through the mouth. As vomiting proceeds, the stomach contracts down on the remaining contents, but the main factor in the expulsion is the contraction of the abdominal muscles and diaphragm. In fact vomiting may be excited in an animal in which the stomach has been replaced by a bladder.

NERVOUS MECHANISM OF VOMITING. Normally the action of vomiting is reflex. It can be excited by tickling the back of the throat, when the afferent nerves are the trigeminal and the glossopharyngeal, or by

irritation of the stomach through the afferent fibres of the vagus. But it may be excited reflexly from almost any of the abdominal viscera, *e.g.* uterus, kidney, intestines, etc., through the labyrinth or eyes, as is supposed to be the case in the vomiting of sea-sickness, and it is a marked symptom in many cases of disease of the cerebrum and cerebellum. The efferent impulses are carried by the vagi to the stomach, by the phrenics to the diaphragm, and by the various spinal nerves to the abdominal muscles. There are also inhibitory impulses descending the vagi to the œsophagus and cardiac sphincter. The reflex act depends on the integrity of the medulla, so that a 'vomiting centre' is sometimes said to be situated in the medulla.

Drugs may produce vomiting either by irritating the stomach, *e.g.* mustard and water, zinc sulphate, ipecacuanha, or by direct action on the medullary centres, *e.g.* apomorphine, etc.

INTESTINAL DIGESTION

The products of gastric digestion are passed at intervals into the first part of the duodenum. Here they meet the secretions of the pancreas, the liver, the tubular glands of the intestine, and the secretion of Brunner's glands, which are situated at the very beginning of the duodenum. The glands of Brunner extend only over about half to one and a half inches in the carnivora, such as the dog or cat, but in the herbivora they may be found occupying the upper six inches of the intestine. The secretion of these various juices is practically simultaneous and is aroused by the very act of entry of the acid chyme into the duodenum. Although they co-operate in their action on the foodstuffs, it will be convenient to deal separately with each, both as regards their action and the mechanism of their secretion.

THE PANCREATIC JUICE

Pure pancreatic juice can be obtained, from an animal with either a permanent or temporary fistula, by the injection of secretin into the animal's veins. A flow of pancreatic juice may also be produced by the administration of pilocarpine, but the pancreatic juice obtained by its injection is richer in organic solids and enzymes than that obtained by the injection of secretin. The average composition of pancreatic juice is shown in the following Table :—

	A	B		C
		(a)	(b)	
Alkalinity :				
Number of c.c. $\frac{N}{10}$ NaOH equal to } 10 c.c. juice	12.7	12.4	9.0	5.5
<i>I.e.</i> in terms of Na in 100 c.c. }	0.29	0.28	0.26	0.12
Total solids in 100 c.c. }	1.6 1.56	2.25	1.5	6.38 6.40
Total proteins in 100 c.c. }	0.5 1.00	—	—	4.8
Ash in 100 c.c. }	0.92 0.28	1.00	1.00	1.3
Chlorides in 100 c.c. }	0.30	—	—	0.27
Total nitrogen }	—	—	—	0.74

A. Secretin juice from three dogs. Sp. gr. 1014.

B. Secretin juice, specimen collected at beginning (a), and at end (b).

C. Pilocarpine juice.

Secretin juice is a clear or slightly opalescent fluid, alkaline ($pH = 8.7-8.9$) from the presence of sodium bicarbonate, its alkalinity varying between $\frac{N}{10}$ and $\frac{N}{7}$ alkali. It is therefore about as alkaline as gastric juice is acid.

The proteins of the juice may be roughly divided into three groups, a small amount of nucleo-protein precipitated on acidification, a protein coagulating at $55^{\circ}C.$, and another at about $75^{\circ}C.$ The juice tends to become poorer in proteins and enzymes, but not in alkali, as secretion proceeds. The concentrated juice obtained by injection of pilocarpine, which may contain as much as 6 per cent. total solids, is always considerably less alkaline and richer in enzymes than the more dilute juice got by injection of secretin. The most interesting and important constituents of the juice are its enzymes. The juice on arrival in the intestine has, or develops, an effect on all three classes of foodstuffs: proteins, fats and carbohydrates, due to the presence of distinct enzymes, viz. trypsin, steapsin or lipase, and amyllopsin.

THE ACTION OF PANCREATIC JUICE ON PROTEINS. Although the digestive action of pancreatic juice on proteins was pointed out by Corvisart, little attention was paid to this effect until Kühne subjected the action of extracts of the gland to a thorough investigation. The failure of Claude Bernard to observe this action must be ascribed to the fact that he worked with pure pancreatic juice. This juice as secreted is free from proteolytic effects, and for the development of this power it is necessary that some change should be brought about in the juice itself, namely the change known as activation. This change under normal circumstances is effected directly the juice enters the gut, by the action of a substance—enterokinase—contained in the succus entericus. The pancreatic juice thereby acquires a proteolytic activity superior to that of any other digestive juice, so that the proteins of the food undergo a very thorough hydrolysis. The different constituents of the protein molecule show a varying resistance to the action of trypsin. The greater part of the molecule is rapidly broken down into its proximate constituents, amino-acids; and the same change is undergone by the proteoses and peptones resulting from the gastric digestion of proteins. Within a few minutes, therefore, after the chyme has reached the small intestine, a certain amount of amino-acids will have been formed. Some of the products present a resistance to disintegration. After tryptic digestion for a few hours, the mixture will be found still to contain a considerable quantity of peptone, which in consequence of its resistance to further alteration was designated by Kühne ‘antipeptone.’ This certainly included some of the diamino-acids, which at that time had not been isolated. There is always a part, however, which gives the biuret reaction and is only slightly broken down after the prolonged action of trypsin. Even when the trypsin has acted for weeks, and the biuret reaction has entirely disappeared, the mixture will be found to contain, in addition to the separate amino-acids, some members of the polypeptide class. One of these polypeptides has been isolated by Fischer and Abderhalden from the products of tryptic digestion of the protein of silk, and has been found to contain glycine, alanine and proline. The stages in tryptic digestion, *e.g.* of fibrin, may be set out as follows:

(1) After one hour’s digestion—soluble coagulable protein, deutero-albumose, peptone, amino-acids, with a small amount of alkali metaprotein produced by the action of the alkali of the juice.

(2) After digestion for one day—deutero-albumose, ‘antipeptone,’ amino-acids, polypeptides.

(3) After digestion for one month—amino-acids, polypeptides.

Among the amino-acids, tyrosine is one of the first to be split off, and this substance, with leucine, was among the earliest known products of pancreatic digestion. The action of trypsin is thus seen to resemble very closely the action of boiling concentrated hydrochloric acid. Like the latter it attacks the protein molecule at the CO-NH -coupling, introducing water at this point and therefore breaking up the polypeptide groupings into simple amino-acids. Why it always leaves a certain remnant of the polypeptides unattacked is not at present explained. The investigation of its action on the polypeptides has shown that very minute differences in the grouping of the molecule may determine whether or not the molecule is attacked by trypsin. Apparently it will only attack such molecules as are present in the naturally occurring proteins. Thus, under the action of trypsin the following polypeptides undergo hydrolytic dissociation: alanyl glycine, alanyl alanine, alanyl leucine A; while the closely similar polypeptides, glycyl alanine, glycyl glycine, alanyl leucine B, are left untouched.

CONDITIONS OF TRYPTIC ACTIVITY. Since the pancreatic juice is alkaline, it might be expected that trypsin would be most effective in an alkaline medium. It must be remembered, however, that the alkaline juice, when secreted, meets the correspondingly acid contents discharged from the stomach, and that the resulting mixture is practically neutral. This neutrality exists throughout the small intestine. On investigating the action of trypsin outside the body, it is found that, at any rate as concerns its earlier stages, this enzyme is more active in the presence of sodium carbonate. It is usual to make up an artificial digestive mixture by dissolving commercial trypsin in 0.2 to 0.3 per cent. sodium carbonate. The optimum amount of sodium carbonate depends on the strength of the solution in trypsin: the more trypsin present the higher is the optimum amount of sodium carbonate. It is stated that, although an alkaline reaction is more advantageous for the earlier stages of tryptic activity, the later stages take place best in a neutral medium. This result is probably due to the fact that trypsin in alkaline medium is extremely unstable, so that, when prolonged digestions are carried out, the trypsin would be rapidly destroyed if the medium were strongly alkaline. The destructibility of trypsin, as well as its action, is largely affected by the presence of proteins or their digestion products in solution. Bayliss has adduced evidence to show that, when trypsin acts upon protein, it enters into some form of combination with the protein molecule. This combination protects the trypsin from the destructive action of alkali. The velocity of the reaction gradually diminishes, owing probably to a combination of the trypsin with the products of digestion, and its consequent removal from the sphere of action. If by any means the amino-acids be removed, the action of the trypsin is renewed. Destruction of the enzyme occurs in the intestine itself. If the intestinal contents be collected by means of a fistula at the lower end of the ileum, they show little or no proteolytic activity.

THE ACTIVATION OF PANCREATIC JUICE. Fresh extracts of pancreas, or freshly secreted pancreatic juice collected straight from the duct without contact with the intestinal mucosa, have no digestive action on egg-white, though able to digest peptone, histone or protamines. It was shown by Pavlov and Chepovalnikov that the normal development of the activity of the juice was due to the action of a constituent of the succus entericus which they named *enterokinase*. This substance, according to Waldschmidt-Leitz, is an activator, which combines in definite proportions with the inactive enzyme (formerly called trypsinogen) to form the activated enzyme, trypsin. The activation proceeds most rapidly in neutral solution,

and the amount of activation depends on the quantity of enterokinase added, though the length of time required to reach full activity is roughly constant (half an hour).

This view is in conflict with that held by Pavlov, and by Bayliss and Starling, who regarded enterokinase as an enzyme which acted on a precursor, trypsinogen. Strong evidence in favour of the activation view is, however, provided by the observation that when active trypsin is shaken with colloidal alumina in acid solutions, it is re-converted into the inactive form, and the enterokinase is adsorbed by the alumina, from which it can be recovered by treatment with dilute ammonia or alkaline phosphate solutions; on mixing the inactivated solution with this extract the activity is restored. Partial separation of the two components in active trypsin can also be effected by ultra-filtration through collodion, the inactivated form passing through. If pancreatic juice be allowed to stand, even with the addition of toluene to prevent bacterial infection, it gradually acquires a certain degree of activity. If, however, sodium fluoride be used as an antiseptic, the juice remains permanently inactive. The spontaneous activation of the juice may be hastened by neutralisation. The most potent means next to enterokinase is the addition of lime salts. If a few drops of 10 per cent. calcium chloride solution be added to fresh pancreatic juice, the calcium being in such a quantity as to suffice to combine with all the carbonate present in the juice, complete activation of the juice occurs within a couple of days. According to J. Mellanby, the calcium acts simply by neutralising the juice and thus allowing minute traces of enterokinase already present in the juice to exert their effect. It is not likely that this calcium activation plays any part in the normal processes of digestion, since for its completion it needs twelve to sixteen hours, whereas the enterokinase present in the succus entericus will effect the activation of the juice within a few minutes.

THE ACTION OF PANCREATIC JUICE ON MILK. On the addition of pancreatic juice to milk, a clot is produced which speedily redissolves. If re-solution takes place too rapidly the production of a formed clot may be missed. Since the milk-curdling action is proportional to the proteolytic activity of the juice, and is not present, for instance, in fresh juice not activated by enterokinase; and since a similar clotting action is seen as the first stage of the action of other proteolytic enzymes, it seems probable that this phenomenon is not due to the presence of a specific milk-clotting enzyme, but is one of the actions of trypsin.

THE ACTION OF PANCREATIC JUICE ON CARBOHYDRATE. The pancreatic juice, as well as fresh extracts of the pancreas itself, contains a strong amylolytic enzyme, diastase, amylase or amyllopsin. If a few drops of pancreatic juice be added to a 1 per cent. solution of boiled starch, within a few seconds the solution clears, and in half a minute, on the addition of iodine, a red colour is obtained, showing the presence of erythro-dextrin. At the end of a few minutes no colour is produced with iodine, and the solution contains maltose. The stages in the hydrolysis of starch brought about with pancreatic juice are exactly similar to those effected by ptyalin. If the juice be neutralised, the process of hydrolysis goes on to the formation of glucose. This further conversion is due to the presence in the juice of a second enzyme—maltase—which converts the disaccharide maltose into the monosaccharide glucose. The juice in the gut is therefore able to effect the further digestion of the products of salivary digestion. On the other disaccharides pancreatic juice is without effect. It contains no invertase, nor does it, in spite of certain statements to the contrary, ever contain lactase. It has therefore no effect on either cane sugar or lactose.

THE ACTION OF PANCREATIC JUICE ON FATS. Fresh pancreatic juice contains a strong lipase or fat-splitting enzyme, by means of which, in the presence of water, neutral fats are broken up into

glycerin and the corresponding fatty acids. This enzyme is active either in an alkaline, neutral or very slightly acid medium. If the reaction be alkaline, the fatty acids produced by the lipolysis combine with the alkali present, with the formation of soaps. The enzyme may be obtained from extracts of the fresh gland, but is rapidly destroyed if active trypsin be present. It is also contained in some of the dried commercial preparations of trypsin. It is apparently insoluble in distilled water, and is therefore found in the residue after extracting these commercial preparations with water. It is easily soluble in glycerol. The velocity with which lipolysis occurs is much increased (four to five times) by the addition of bile. This adjuvant action of bile is not destroyed by boiling, and is due entirely to the bile salts. These act in two ways: In the first place, by their physical qualities they diminish the surface tension between water and oil, so enabling a closer contact to be effected between the watery solution containing the juice and the oil which is presented to it. Moreover, they may aid in the solution of the enzyme itself. In the second place, bile salts have a solvent action on soaps as well as on fatty acids in slightly acid medium. Bile may be regarded, therefore, as a favourable excipient or medium for the interaction of the lipase and the neutral fats. The lipase of pancreatic juice will also hydrolyse other esters of fatty acids, such as ethyl butyrate or monobutyryl. On the phosphorised fats or phosphatides, such as lecithin, its action is still a subject of doubt. According to certain authors, extracts of the pancreas have the power of splitting off choline from lecithin. It is not known whether the same property is present in pancreatic juice itself, or whether any other dissociations are brought about in the complex molecule of lecithin under the action of this digestive fluid.

THE SECRETION OF PANCREATIC JUICE

In order to study the relation of the secretion of pancreatic juice to the other processes of digestion, observations must be carried out on an animal with a permanent pancreatic fistula.

The most satisfactory method of accomplishing this was devised by Pavlov. The pancreas in most cases possesses two ducts, the upper one often opening along with the bile duct, the lower one a short way down. The relative sizes of these two ducts vary in different animals, the lower one being larger in the dog, while in man and the cat the upper one is larger. In order to establish a pancreatic fistula in a dog, a small piece of the duodenal wall is excised, having the papilla of the lower duct opening in the middle of its mucous surface. The integrity of the gut is restored by suturing the margins of the wound in the duodenum, and the excised piece is brought to the surface and stitched in the middle of the abdominal wound. The greater part of the pancreatic secretion will escape by the fistula, and can be collected either by the insertion of a cannula into the duct or by attaching a glass funnel below its orifice. Great care has to be taken in the after treatment of such animals. The duct must be dilated each day with a bougie to prevent cicatrization. The pancreatic juice, which flows over the papilla, acquires in so doing strong proteolytic powers, and tends therefore to digest and irritate the adjacent abdominal wall. This can be prevented by taking care to remove the papilla and exposed duodenal mucosa as soon as the graft has healed on to the surface. Another drawback is that the continual loss of pancreatic juice in many cases seriously affects the animal's health. This may be obviated to a certain extent by keeping the animal on a milk diet with the addition of sodium bicarbonate to replace the loss of this salt by the juice. With great care, Pavlov has succeeded in keeping such animals in a perfectly healthy condition.

Clinical observations of human pancreatic fistulae have confirmed the experiments made on dogs.

In the fasting condition there is for long periods (one to two hours) no expulsion of juice from the duct. Probably, however, there is a very slow

secretion of juice, which is expelled from the duct with the occurrence of periodical activity of the alimentary canal (Babkin), so that the escape of a few drops may be observed at long intervals. If a meal be administered to the animal, a flow of juice begins in one to two minutes. From this time there is a steady, slow rise of the rate of secretion, which lasts for two to three hours, and then gradually diminishes. The greatest increase in flow is observed at the time when the first portions of digested food escape from the stomach into the duodenum. The secretion must therefore be determined in some way by the entry of this food into the duodenum. By experiments on dogs possessing a gastric as well as a pancreatic fistula, it has been shown that the introduction of acid, *e.g.* 0.4 per cent. HCl, into the stomach evokes, as soon as it passes into the duodenum, a rapid flow of pancreatic juice. A similar but smaller effect is produced by the passage of oil from the stomach into the duodenum. The introduction of alkalies is without influence. Weak acids are also effective exciters of secretion if they be introduced directly into the duodenum itself or into a loop of small intestine. The secretion produced gradually diminishes as the loop employed comes nearer to the cæcum, and as a rule the injection of dilute acid into the lower foot or eighteen inches of ileum is without effect on the pancreas. The striking resemblance between the secretion thus evoked and that produced in the salivary glands by injection of acid into the mouth suggests that we have here to do with a reflex secretion, but we now know that, although the secretion of pancreatic juice is under nervous control, this response to acid in the duodenum is not due to a reflex, but to a humoral (chemical) mechanism.

The pancreas receives fibres from the vagi as well as from the splanchnic nerves (sympathetic system). Pavlov noticed that if, in an animal with a permanent fistula, the vagus on one side were cut and left for four days in order to allow the cardio-inhibitory fibres to degenerate, prolonged stimulation of the peripheral end of the nerve evoked a flow of pancreatic juice. He obtained the same results by stimulating this nerve below the point at which it had given off its cardio-inhibitory fibres, in animals in which the reflex inhibitions from the operation itself were prevented by total section of the medulla. Pancreatic secretion also resulted from vagus stimulation when every care was taken to prevent acid stomach contents being expelled into the duodenum by contraction of the stomach wall; *e.g.* when the pylorus was ligatured and the stomach filled with an alkaline solution. There can be no doubt that the vagus is a secretory nerve to the pancreas, and that reflex secretion of pancreatic juice occurs within a minute or two of the taking of food. The juice obtained by vagus stimulation is glairy, very concentrated in solids, and rich in enzymes. Under certain circumstances Pavlov also obtained secretion on stimulation of the splanchnic nerves. When secretion has been established by prolonged and repeated stimulation of one vagus, a stimulation of the other vagus at first checks it. This has been supposed to demonstrate the presence of secretory inhibitory fibres in the vagus, but it is more probable that the stoppage of secretion is due to constriction of the ducts. (ANREP).

It was at first believed that a reflex secretion was set up by the introduction of acid into the duodenum. It was shown later, however, by Popielski and by Wertheimer that the injection of acid into a loop of small intestine was followed by secretion of juice even after section of both vagi and destruction of the sympathetic ganglia. On repeating these experiments Bayliss and Starling found that a secretion of juice was produced even when the acid was introduced into a loop of the small intestine entirely freed from any possible nervous connections with the rest of the body. It was evident, there-

fore, that the stimulus from the intestine to the pancreas, which causes the secretion of the latter, must be carried, not by the nervous system, but by the blood stream. The injection of acid into the portal vein was without effect on the pancreas, but on pounding up some scrapings of the intestinal mucous membrane with dilute hydrochloric acid and filtering, and injecting the filtrate, a copious flow of pancreatic juice was produced. This chemical messenger, or hormone, from the intestine to the pancreas is called 'secretin,' or 'pancreatic secretin.' That it is present in the mucous membrane is shown by the fact that secretin can be extracted by the action of acids or by the prolonged action of alcohol from mucous membrane which has been killed by heat.

Secretin may also be obtained from intestinal mucous membrane by treating this with solutions of soap, water, or dilute alkali, so that it is probably preformed there.

In order to prepare it, the mucous membrane is ground up with sand, boiled with 0.4 per cent. hydrochloric acid, and then neutralised while boiling by the cautious addition of sodium hydrate or sodium acetate. The coagulable proteins are in this way precipitated, and the filtered solution contains the secretin.

J. Mellanby has obtained very powerful preparations of secretin by extracting the duodenal mucosa with alcohol, distilling off the alcohol *in vacuo*, acidifying and adding bile salts. The bile salts are precipitated and carry down the secretin. This precipitate is dissolved in alcohol and reprecipitated by adding acetone. The secretin is a readily soluble substance resembling a polypeptide, and is rapidly destroyed by pepsin and trypsin. It diffuses slowly through animal membranes. Though stable in acid solutions, it is very rapidly destroyed in alkaline or neutral solutions, especially under the influence of bacteria. It is apparently oxidised with extreme ease.

In this secreting mechanism we have an example of a correlation effected by chemical means, between the activities of two different portions of the body. The acid chyme enters the first part of the duodenum. Immediately a certain amount of secretin is extracted by the acid, is carried by the blood stream to the cells of the pancreas and excites there the secretion of strongly alkaline pancreatic juice. As soon as sufficient juice has been secreted to neutralise the acid chyme, the formation of secretin, and therefore the further secretion of alkali, comes to an end. If the stomach still contains food, however, the process is renewed. So long as the contents of the duodenum are acid, the pylorus remains firmly closed. As soon as these are neutralised, the pylorus relaxes and allows the entrance of a further portion of acid chyme. Thus the whole chain of processes goes on until the stomach is empty and all its contents have passed into the intestine.

An important part appears to be played by the presence of the bile salts in the intestine, since Mellanby has found that the introduction of bile, or bile salts together with acid, gives rise to a particularly profuse secretion; the secretin and bile salts are possibly absorbed together.

The secretin mechanism provides alkali for the neutralisation of the acid stomach contents. But the nervous mechanism provides the enzyme content of the juice, so that, even when for any reason the gastric contents are not acid, pancreatic digestion is still possible. (J. MELLANBY.)

The amount and activity of pancreatic juice obtained after a meal varies with the nature of the latter. The differences seem largely determined by the amount of acid secreted in the stomach and passed on to the duodenum, and by the presence of specific excitants, such as fat and soap, which raise the enzyme content of the juice. It was suggested by Walther that there was a qualitative alteration in the constitution of the juice according to the nature of the food ingested, that, *e.g.*, excess of protein causes an increase of the trypsin while excess of carbohydrate would cause an increase in the amylase of the juice. Later researches have failed to confirm this view; though

qualitative variations have been shown to occur, these do not appear to be such as to adapt the secretion to the food. Apparently when the pancreas is excited to secrete, it turns out its various enzymes in constant proportion, depending on the amounts of these already present and stored up in the gland.

THE STRUCTURAL CHANGES IN THE PANCREAS ACCOMPANYING SECRETION

Kühne and Sheridan Lea observed the gland of the rabbit in a living state under the microscope. They noted that activity, excited by pilocarpine, was associated with

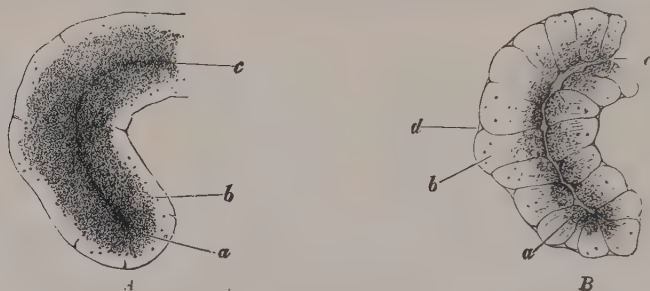


FIG. 312. A Terminal Lobule of the Pancreas of the Rabbit. (KÜHNE and SHERIDAN LEA.)

A. In resting condition.

B. After active secretion.

a discharge of granules, a clearing up of the cells, and a diminution in size and the appearance of a lumen to the gland alveoli (Fig. 312). A normal resting gland is of an opaque, yellowish-white colour and of firm consistence. On section it is seen to consist



FIG. 313. Alveoli of Dog's Pancreas. (BABKIN, RUBASCHKIN and SAVITSCH.)

A. Resting. B. After moderate secretion with discharge of granules.

of numerous secreting alveoli, the cells of which present two well-marked zones: a narrow peripheral zone in which the nucleus is embedded, which is strongly basophile; and a central zone which is turned towards the lumen, occupying two-thirds or three-quarters of the cell, and is closely packed with highly refractive granules strongly oxyphile and presumably composed of or containing the precursors of the various constituents of the pancreatic juice (Fig. 313 A). If injection of secretin be continued until the rate of secre-

tion evoked by each injection diminishes considerably, marked changes are observed. The gland is now pink, transparent, moist and soft. On section the lumen of each alveolus is enlarged, the cells are shrunken, and the granules are found to lie only along the border of the cell turned towards the lumen, the rest of the cell, which is much reduced in size, being made up of the basophile protoplasm. Even greater effects are observed after long continued stimulation of the vagus (Fig. 313 B).

THE LIVER AND BILE

The liver, the largest gland in the body, is, like the other glands associated with the alimentary tract, formed in the embryo by an outgrowth of the hypoblast lining the alimentary canal. At first it resembles in structure other secreting glands, such as the pancreas, being composed of branched tubules which pour their secretion into a common duct. In the adult, however, the relation of the liver cells to the ducts is entirely subordinated to their relation to the blood vessels of the organ, and it requires special histological methods to make out the relations between the liver cells and the bile ducts.

The liver, on section, is seen to be divided up into lobules composed of columns of polygonal cells, radiating from the centre. The portal vein, which drains the blood from the alimentary canal, breaks up into branches which lie at the periphery of the lobules, forming the interlobular veins, and which send off numerous capillaries which pass inwards between the columns of cells to join the intralobular vein lying at the centre of the lobule. From the intralobular the blood passes by the large sublobular vein into the hepatic veins and inferior vena cava. In an injected specimen it is easy to see that every liver cell is adjacent to at least one blood capillary. The portal vein conveys only venous blood to the liver. In order to supply oxygen to the working liver cells, this organ receives a supply of arterial blood by the hepatic artery. The branch of the hepatic artery runs with the branches of the portal vein in the connective tissue of Glisson's capsule surrounding the lobules, and breaks up into capillaries which are in free communication with the capillaries derived from the portal system.

As might be expected from its structure, the secretory functions of the liver represent but a small proportion of its activities in the body. The liver is in fact the greatest chemical factory of the body, receiving by the portal vein the products of digestion as they are absorbed from the alimentary canal. It converts these into other substances, breaking them down or building them up according to the needs of the body as a whole. Thus, when carbohydrates are being absorbed in quantity, it converts the glucose contained in the portal blood into glycogen which it stores up, reconverting the latter into glucose and letting it loose into the circulation when this substance is required by the body tissues. The liver may also, as we shall see later, convert the products of protein digestion into sugar. In the same way the liver plays an important part in the metabolism of proteins and of fats, so that its functions will have to be dealt with in the various chapters concerned with the fate of the different foodstuffs and different constituents of the animal body. In this chapter we are merely concerned with its action as a secreting gland. In addition to its function in digestion, the bile must also be regarded as an excretion, representing, as it does, the channel by which the products of disintegration of hæmoglobin are got rid of from the organism. As an excretion, the production of bile must be continuous and related, not to the processes of digestion, but to the intensity of destruction of the red corpuscles. On the other hand, bile as a digestive fluid is needed in the gut only during the period that digestion is going on. The exigencies of the body therefore require a continuous excretion, but a discontinuous entry of this fluid into the small intestine. This is secured, in the majority of animals, by the existence of the gall bladder, in which all bile,

secreted during the intervals between the periods of digestive activity, is stored up. In the horse, where the gall bladder is absent, its place is taken to some extent by the great size of the bile ducts. Since the bile accumulates in the gall bladder during the whole time that digestion is not going on, and is only poured into the gut during digestion, in a fasting animal the gall bladder is distended, whereas in an animal some hours after a meal the gall bladder is less full.

During the period that the bile remains in the gall bladder it undergoes certain changes, as shown by comparison of the composition of human bile obtained from the gall bladder with that obtained from a fistula of the bile duct.

ANALYSES OF BILE (HUMAN) [per cent.]			
From a biliary fistula (Yeo and Herroun)		From the gall bladder (Czyhlarz <i>et al</i>)	
Mucin and pigments	0.15	Mucin	1.64
Sodium taurocholate	0.06	Bile Pigments	0.16
Sodium glycocholate	0.16	Bile Salts	4.67
Cholesterol	0.04	Cholesterol	0.66
Lecithin		Lecithin	0.56
Inorganic salts	0.84	Inorganic Salts	0.85
Water	98.72	Water	90.57

The inorganic salts are mostly sodium chloride and bicarbonate, the fixed CO_2 of the bile varying from 10 to 60 volumes per cent. The reaction of liver bile in the hepatic ducts is usually slightly alkaline (pH 7.7), while in the gall bladder it is slightly acid (pH 6.8) as a rule.

During its stay in the bladder the bile is rapidly concentrated by the loss of water and by the addition to it of mucin or nucleo-protein, derived from the cells lining the bladder. The speed with which the gall bladder concentrates the bile is remarkable, the total solids of bladder bile reaching as much as ten times that of fistula bile, and the volume showing a corresponding reduction.

The Bile Salts.—Characteristic of bile are the so-called “bile salts,” which give the well-known Pettenkofer reaction—a purple colour with cane sugar and strong sulphuric acid. The bile salts are sodium salts of complex acids, chiefly glycocholic and taurocholic acids. Both acids are present in human bile, but in the bile of the dog and the sheep only taurocholic acid is found. These acids themselves are complex compounds of an important bile acid, cholalic, or cholic acid, and can readily be resolved by hydrolysis with acids into their proximate constituents thus:—

Glycocholic acid = glycine + cholalic acid

Taurocholic acid = taurine + cholalic acid.

Taurine is amino ethyl sulphuric acid, $\text{NH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{SO}_2\cdot\text{OH}$, and is probably derived in the body from the metabolism of cysteine or cystine.

Cholalic acid ($\text{C}_{24}\text{H}_{40}\text{O}_5$) and the closely-related bile acids (desoxycholic or choleic acid, $\text{C}_{24}\text{H}_{40}\text{O}_4$ and lithocholic acid $\text{C}_{24}\text{H}_{40}\text{O}_3$) are organic acids of high molecular weight and considerable structural complexity. On dehydration and subsequent reduction they all yield cholanic acid, $\text{C}_{24}\text{H}_{40}\text{O}_2$. Cholanic acid or its isomer, isocholanic acid, can be obtained from cholesterol by reduction, and subsequent oxidation with chromic acid. It is thus clear that the bile acids are chemically closely related to cholesterol.

Though this is so, and although it is probable that the bile salts are produced in the liver, there is no conclusive evidence for this, and very little for the supposition that, in the body itself, cholic acid is actually derived from cholesterol.

When cholic acid is administered, there is an increased excretion of bile

salts, provided the necessary taurine is also given or made available, as is the case if a liberal protein diet is given at the same time. Even in fasting animals, however, there is a constant production of bile salts, though in smaller amount.

The Bile pigments, bilirubin and biliverdin, are waste products. They pass into the intestine, and are there converted by the processes of bacterial reduction into stercobilin, which is excreted for the most part with the fæces, a small proportion being perhaps absorbed into the blood vessels and turned out in a more or less altered condition as the pigments of the urine. From the point of view of digestion, the important constituents of bile are the '*bile salts*,' with the lecithin and cholesterol held in solution by these salts. The time relations of the secretion, as well as of the flow of bile into the intestine in connection with the processes of digestion, can be learnt from animals or men in which the bile is conducted to the outside of the body by means of a permanent fistula.

For this purpose Pavlov has devised the following operation: In the dog the abdomen is opened, and the common bile duct sought as it passes through the intestinal wall. The orifice of the duct, with a piece of the surrounding mucous membrane, is cut out of the wall of the intestine, and the aperture thus made sutured. The excised portion of mucous membrane, with the opening of the duct, is then sewn on to the surface of the duodenum, and the loop of duodenum at this point is stitched into the abdominal wound. After healing, the natural orifice of the bile duct is thus made to open on the surface of the abdomen.

In an animal treated in this way the flow of bile from the fistula is found to run parallel to the pancreatic secretion. Although smaller in amount, it rises and falls with the latter. Thus a meal of meat produces a large flow of bile, a meal of carbohydrates only a small flow. Moreover, beginning almost immediately after taking food, it attains its maximum, as does the pancreatic juice, in the third hour and then rapidly declines.

In the production of this flow of bile, two factors may be involved: (1) the emptying of the gall bladder; (2) an increased secretion of the bile. By collecting the bile direct from the hepatic ducts we find that, synchronously with the great outpouring of bile during the third hour after a meal, there is an increased secretion of this fluid. The passage, therefore, of the semi-digested food from the stomach into the duodenum causes, not only a slow contraction and emptying of the gall bladder, but also an increased secretion of bile by the liver. What is the mechanism involved in the production of these two effects? The muscular wall of the gall bladder shows rhythmic contractions, and, as has been shown by Dale, is under the control of nerves derived both from the vagus and from the sympathetic, the former conveying motor and the latter inhibitory impulses, while the sphincter (of Oddi) receives branches from the same source, but having the opposite effects. It was once supposed that the entry of acid chyme into the duodenum reflexly provoked a contraction of the gall bladder and relaxation of the sphincter; but it is not certain that there is a direct correlation between the two. There are at present two schools of thought: (1) that the gall bladder empties itself by active contraction, resulting from a chemical stimulus in the blood; (2) that emptying occurs during the intermittent relaxation of the sphincter between the duodenal peristaltic waves, as the result of the steady tonus of the gall bladder musculature.

There is almost certainly a hormone acting on the gall bladder, liberated into the blood by the presence of food in the duodenum; fat and egg yolk are the most active substances in this connection, even more so than acid. Ivy and Oldberg have extracted from the duodenal mucosa a secretin-like substance which stimulates contraction of the gall bladder.

The alterations occurring in the size of the gall bladder can be most readily observed clinically by the administration of tetra-iodo-phenolphthalein, which is excreted in the bile and is opaque to the X-rays (Graham-Cole test).

The increased *secretion* of bile can also be evoked by the introduction of acid, such as 0.4 per cent. HCl, into the duodenum, even after division of all connections between the liver and the central nervous system. It also occurs on intravenous injection of secretin. Since the presence of bile is necessary for the full development of the activities of the pancreatic juice, it is not surprising that its secretion is initiated by the same sort of stimulus. In one experiment, for instance, the injection into the veins of 5 c.c. of a solution of secretin increased the secretion of bile by the liver from twenty-seven drops in fifteen minutes to fifty-four drops in fifteen minutes.

The most potent effect in increasing bile secretion, however, is the presence of bile salts in the intestine, the active constituent being the cholalic acid. Intravenous injection of this gives a large increase in the flow of bile. The normal mechanism seems to be that the contraction of the gall bladder liberates bile into the duodenum, and bile salts are then absorbed into the blood. This, besides promoting pancreatic secretion, as already explained, also accelerates the secretion of bile, and bile salts given *per os*, or intravenously, can be recovered quantitatively from the bile secreted during the ensuing few hours. There is no conclusive evidence in favour of the suggestion that bile pigments may also circulate in a similar way from intestine to blood and be re-excreted in the bile.

THE DIGESTIVE FUNCTIONS OF THE BILE. The digestive functions of bile are due, not to the presence of enzymes, but to the peculiar influence of the bile salts on the actions of the pancreatic juice. Most important is the part played by the bile in the digestion and absorption of fats. The fat-splitting action of pancreatic juice is trebled by the addition of bile, whether boiled or unboiled. This quickening action of the bile probably depends, like its function in the absorption of fats, on the peculiar physical properties of the bile salts, and of the lecithin and cholesterol which they hold in solution. Not only does such a solution diminish the surface tension between watery and oily fluids, so promoting emulsification, and thus the closer approach of the lipase of the pancreatic juice to the fats on which it is to act, but it has also the power of dissolving fatty acids and soaps, including even the insoluble calcium and magnesium soaps. Once an emulsion of fat has been formed with the aid of the bile salts, this is stabilised by various accessory agents, mucin, soaps, proteoses, &c. Further, the bile salts definitely function as activators of pancreatic lipase, even when this acts on substances in solution. It is possible that this activating effect is due to the bile salts in some way bringing the enzyme and substrate into sufficiently close contact with one another. It has been shown by Nicloux that the lipase contained in oily seeds, such as those of the castor oil plant, is insoluble in water, but soluble in fatty media. The dried material obtained from the pancreas in many cases yields no lipase to water, but gives a strongly lipolytic solution when extracted with glycerol. The digestive function of bile, therefore, lies in its power of serving as a vehicle for the suspension and solution of the interacting fats, fatty acids, and fat-splitting enzyme. This vehicular function plays an important part in the absorption of fats. These pass through the striated basilar membrane bounding the intestinal side of the epithelium, either in a fine state of suspension (an emulsion), or dissolved in the bile in the form of fatty acids, or as soaps and glycerol (but see p. 606). On the arrival of these products of digestion in the epithelial cells, a process

of resynthesis is set up. Droplets of neutral fat make their appearance in the cells, whence they are passed gradually into the central lacteal of the villus and so into the lymphatics of the mesentery and into the thoracic duct. The bile salts thus released from their function as carriers are absorbed by the blood circulating through the capillaries of the villi, and carried by the portal vein to the liver. On arrival they are once more taken up by the liver cells and turned out into the bile. Owing to the fact of their ready excretion by the liver cells, bile salts are the most reliable cholagogues with which we are acquainted. By this circulation of bile between liver and intestine, the synthetic work of the liver in the production of the bile salts is reduced to a minimum, and it has only to replace such of the bile salts as undergo destruction in the alimentary canal under the influence of micro-organisms, and are lost to the organism by passing out in the fæces as a gummy amorphous substance known as *dyslysin*. The action of pepsin is checked by bile owing to its inclusion in a precipitate which is thrown down.

The effect of various diets on the secretion of bile has been studied by Barbera. He finds that, whereas the secretion of bile is greatest on a meat diet, it is somewhat less on a diet of fat, and is insignificant on a purely carbohydrate diet. That is to say, the secretion of bile is greatest on those diets the digestion of which is attended by the passage of a large amount of acid chyme or of oil into the duodenum. Oil is almost as efficacious as acid in promoting the production of secretin in the living duodenum.

JAUNDICE. If the bile ducts are ligatured, or obstructed in any way, so as to prevent the entry of bile into the intestine, the bile is reabsorbed and passes by the lymphatics into the blood stream. The bile pigment circulating in the blood is deposited in the various tissues of the body, giving them a yellow colour; bile pigments and bile salts are also excreted with the urine. This condition is known as jaundice. Certain types of jaundice have long been known in which no apparent obstruction of the bile ducts was present. It was therefore assumed that in these cases the bile pigment was set free in the blood, apart from the activity of the liver. Pathologists thus distinguished two kinds of jaundice, hepatogenous and hæmatogenous. The existence of the latter form was long disputed, although it was known that bilirubin could be formed as a product of the disintegration of hæmoglobin in old blood clots. F. C. Mann has succeeded in totally extirpating the liver and, by means of injections of glucose, in keeping the animals (dogs) alive for thirty-six hours. He has found that, six hours after the extirpation, bile pigment begins to accumulate in the blood and in the tissues, showing that this substance can be formed as the result of the disintegration of hæmoglobin without the co-operation of the liver, thus justifying the long-disputed division of jaundice into the two varieties of hepatogenous and hæmatogenous.

This conversion of hæmoglobin into bilirubin occurs in the scattered cells known as the reticulo-endothelial system; these occur in the liver (Kupffer cells), but also in the spleen and other situations.

THE INTESTINAL JUICE

The intestinal juice is mainly secreted by the Lieberkühn's follicles. Besides its activating power on the pancreatic juice, the intestinal juice has numerous other functions to discharge in the digestion of the foodstuffs. In spite of the similarity which obtains between the microscopic structure of the wall of the gut at different levels from duodenum to ileocolic valve, functionally there are many differences between the upper, middle and lower portions of the gut. Speaking generally, we may say that, whereas the processes of secretion are better marked in the upper portions of the gut, absorption predominates in the lower sections, *i.e.* in the ileum. Much of the divergence in the statements which have been made with regard to the factors determining secretion and absorption in the small intestine is due to the failure to appreciate this difference between the activity of the mucous membrane at various levels.

The process of secretion in the small intestine may be studied by isolating loops by means of ligatures, and determining the amount of secretion formed in these loops in the course of a few hours' experiment on an anæsthetised animal. Better results, however, may be obtained by establishing permanent fistulæ, the best type being the Thiry-Vella operation. This consists in cutting out a loop of intestine, and restoring the continuity of the gut by suturing the two ends from which the loop had been excised. Both ends of the excised loop are left open and brought into the abdominal wound. In such a fistula it is easy to introduce substances into the upper end and determine the flow of juice from the lower end, the constant emptying of the loop being provided for by the peristaltic contractions of its muscular coat. Intestinal fistulæ resulting from war injuries have been studied in man by Savitsch, and have given results confirming those made on dogs.

In animals with intestinal fistulæ, a number of different conditions have been found to give rise to a flow of succus entericus, and so far no qualitative difference has been recorded between the upper and lower ends of the gut. A condition which will cause a free flow of juice from a fistula high up in the intestine will generally cause a slight flow from a fistula made from the ileum. Fasting animals show no secretion, or merely a scanty periodic flow about every two hours, from an empty isolated loop. Administration of food is also without regular effect on the isolated loop, so long as this remains empty. An important factor in exciting a flow of juice is local mechanical stimulation: thus the introduction of a drainage tube into the isolated loop is followed by a steady flow of succus entericus, whether the animal be fasting or fed. The flow of juice thus initiated is greatly modified by feeding the animal; thus, a meal of fat will often double the rate of secretion. In most instances, however, the contents of the alimentary canal exert no influence on portions of the intestine with which they are not in contact.

It seems probable that the normal flow of intestinal juice is provoked by the presence, in the intestine, of its normal contents. One of the factors involved is the mechanical stimulus of the contents; the other is probably a local chemical stimulation, which can be effected by various products of digestion. These excitants, which also act on isolated loops, include hydrochloric acid, butyric acid, fats, proteoses, soaps, dextrins, &c.

The response to local mechanical or chemical excitation is apparently brought about through the local nervous mechanism of the intestine (Meissner's plexus), since section of the vagus does not abolish the reaction. The rate of the secretion can, however, be augmented by stimulation of the vagus, though only after a very long latent period (one hour), and the juice obtained by vagus excitation is, unlike that resulting from local mechanical stimuli, very rich in enzymes. (SAVITSCH.)

There are certain facts which seem to speak for an action of the central nervous system in the direction of inhibition of intestinal secretion. Thus it has been observed on many occasions that extirpation of the nerve plexuses of the abdomen, or section of the splanchnic nerve, causes a condition of diarrhoea which may last for two or three days. This condition might be determined either by an increased motor activity of the gut, or by removal of inhibitory impulses normally arriving at the intestinal glands. The latter view receives support from an experiment first performed by Moreau. The abdomen of a dog is opened under an anæsthetic, and three contiguous loops of small intestine are separated by means of ligatures from the rest of the gut. The middle loop is then denervated by destruction of all the nerve fibres lying on its blood vessels as they course through the mesentery, care being taken not to injure the blood vessels themselves. The loops are then replaced in the abdomen and the animal left from four to sixteen hours. On killing the animal at the end of this time, it is often found that the middle loop, *i.e.* the denervated loop, is distended with fluid having all the properties of ordinary intestinal juice, whereas the other two loops are empty. A series of comparative experiments by Mendel and by Falloise have shown that the secretion begins about four hours after the operation, increases for about twelve hours, and then rapidly declines, so that at the end of two days all three loops will be found empty. It is possible, however, that the hyperæmia of the gut, which is

produced by the process of denervation, may be sufficient to account for the increased formation of intestinal juice, since the hyperæmia will tend to pass off as the vessels recover a local tone.

Certain chemical substances introduced into the blood stream, *e.g.* histamine and pilocarpine, produce active secretion of the juice. It is also possible that general humoral mechanisms may play a part, though probably only a subsidiary one, in bringing about normal secretion of succus entericus. Thus Delezenne and Frouin have shown that, in animals provided with a permanent fistula involving the duodenum or upper part of the jejunum, intravenous injection of secretin always causes a secretion of intestinal juice. In the upper part of the gut, therefore, the simultaneous presence of the three juices necessary for complete duodenal digestion is ensured by one and the same mechanism, namely by the simultaneous activity of the secretin, liberated in the intestinal cells by the action of the acid chyme, on pancreas, liver, and intestinal glands. A further chemical mechanism for the arousing of intestinal secretion has been described by Frouin. According to this observer, the flow of juice can be excited by intravenous injection of intestinal juice itself.

A curious fact has been recorded by Savitsch, namely that the production of enterokinase depends upon the contact of the mucosa with pancreatic juice: in an isolated loop the enterokinase slowly disappears, but returns in a few minutes after introduction of pancreatic juice into the loop. The pancreatic juice thus in some way participates in the generation of its own activator.

CHARACTERS OF INTESTINAL JUICE. The intestinal juice obtained from a permanent fistula has a specific gravity of about 1.010. It is generally turbid from the presence in it of migrated leucocytes, disintegrated epithelial cells and clumps of mucus. It contains about 1.5 per cent. total solids, of which 0.8 per cent. are inorganic and consist chiefly of sodium bicarbonate and sodium chloride. It is alkaline in reaction ($pH=8.3$), but less so than the pancreatic juice. The organic matter, besides a small amount of serum albumin and serum globulin, includes a number of enzymes adapted to complete the processes of digestion of the foodstuffs commenced in the stomach and duodenum. It also contains the activator, enterokinase, which we have already studied in detail; its presence is necessary for the development of the full proteolytic powers of the pancreatic juice. An important proteolytic enzyme has been described by Cohnheim under the name '*erepsin*.' Erepsin or some similar enzyme is present in almost all tissues of the body. It is distinguished by the fact that, although it has no power of digesting coagulated protein or gelatin, and only slowly dissolves caseinogen and fibrin, it has a rapid hydrolytic effect on the first products of proteolysis, converting albumoses and peptones into amino-acids—their ultimate cleavage products.

The succus entericus also contains the enzymes *lipase*, *nuclease* and a *phosphatase*. Other enzymes of the intestinal juice are connected with the digestion of carbohydrates. In all mammals the intestinal juice is found to contain *invertase*, which transforms cane sugar into glucose and fructose, and *maltase*, which converts maltose into glucose. In mammals the intestinal mucous membrane also contains *lactase*, *i.e.* an enzyme converting milk sugar into galactose and glucose. Such an enzyme can be extracted from the mucous membrane of all young mammals, but may be very slight or even absent in the intestines of older animals, when it is no longer needed for the ordinary processes of nutrition. By these three enzymes, coming after the digestion of the starches by the amylases of the saliva and pancreatic

juice, it is provided that all the carbohydrate food of the animal is transformed into a hexose, in which form alone carbohydrate can be taken up and assimilated by the cells of the body. The seat of origin of these various substances has been the subject of special investigations by Falloise. Whereas secretin can be obtained from the whole thickness of the mucous membrane, and is probably therefore contained in the epithelial cells covering the villi, as well as in those lining the follicles of Lieberkühn, a superficial scraping of the mucous membrane, which removes only the epithelial cells covering the villi, with the adherent mucus and intestinal secretion, gives a much more active solution of enterokinase than a deeper scraping. The most active solutions of enterokinase are, however, to be obtained from the fluid found in the cavity of the intestine after the injection of secretin. It seems possible that enterokinase is not present as such in the epithelial cells, but is first produced in the process of secretion and formation of the intestinal juice.

The enzymes, *erepsin*, *maltase*, *invertase* and *lactase*, probably pre-exist as such in the epithelial cells, especially in those lining the tubular glands of the gut, since mucous membrane pounded in water yields a solution of these enzymes which is generally more powerful in its action than the succus entericus itself. The enzyme *arginase*, which splits up arginine into urea and ornithine, is only present in the cells. So great is the difference that many physiologists have suggested that the chief action of these enzymes occurs, not in the lumen of the gut, but in the passage of the foodstuffs through the epithelial cells of the small intestine on their way to the blood vessels.

MOVEMENTS OF THE SMALL INTESTINE

The movements of the intestines can be investigated either by direct observation of the gut or by means of the bismuth meal and X-ray examination. In using the former method it is essential to exclude the many disturbing influences which can play on the intestine, either reflexly through the central nervous system or through local reflexes from other parts of the alimentary canal itself. These may be eliminated either by extirpation of the whole of the nerve plexuses of the abdomen, by division of the splanchnic nerves, or by destruction of the spinal cord below the mid-dorsal region. It is questionable, however, whether the movements seen under these conditions are similar to those which occur in the intact animal.

The sum of the evidence at present available indicates that three types of movement occur in the small intestine, namely: (1) Segmenting movements; (2) pendular movements; (3) peristalsis. These three kinds of movements may be seen in an animal treated as described above, when its abdomen is opened in a bath of warm normal salt solution so as to exclude the disturbing influences of drying and cooling.

The *segmenting movements* are the most constant and fundamental. They may be recorded by inserting into the intestine a balloon filled with air and connected with a piston recorder. The constriction which accompanies each contraction is then seen to be most pronounced at the middle of the balloon, *i.e.* in the zone of greatest distension, and the amplitude of the contractions is augmented by increasing the tension of the walls of the gut. These movements are unaffected by the direct application of drugs, such as nicotine or cocaine, which we might expect to paralyse any local nervous structures in the intestinal wall; they occur equally well in the isolated intestine, from which facts Bayliss and Starling concluded that these rhythmic contractions were myogenic, and were propagated from muscle fibre to muscle fibre. This is confirmed by the observation of Gunn and Underhill that the con-

tractions continue in strips of muscle completely freed from any remains of the nerve plexus. These contractions occur with considerable regularity at a frequency which varies inversely with their distance from the stomach, and is of the order of twelve a minute in the ileum. The different frequencies at different levels is due, according to Alvarez, to the existence of a 'metabolic gradient' from above downwards, the upper portions having a higher rate of metabolism and being also more excitable than the lower parts. These contractions must cause a thorough mixing of the contents of the gut with the digestive fluids. On examining under the X-rays the intestine of a cat, which has taken a large meal of bread and milk mixed with bismuth some hours previously, a length of gut may be seen in which the food contents form a continuous column. Suddenly movements occur in this column, which is split into a number of equal segments. Within a few seconds each of these segments is halved, the corresponding halves of adjacent segments uniting. Again contractions recur in the original positions, dividing the newly formed segments of contents and re-forming the segments in the same position as at first (Fig. 314). In this way every particle of

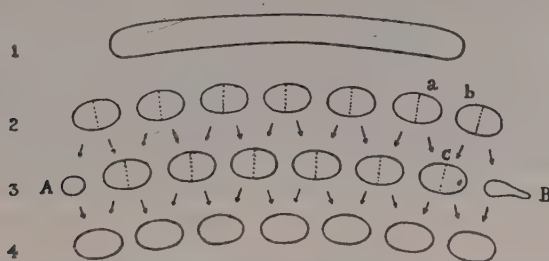


FIG. 314. Diagram of the 'Segmentation' Movements of the Intestines as observed by the Röntgen Rays, after Administration of Bismuth. (CANNON.)

1. A continuous column, intestinal movements being absent.
2. The column broken up into segments.
3. Five seconds later, each segment divided into two, the halves joining the corresponding halves of adjacent segments.
4. Condition (2) repeated five seconds later.

food is brought successively into intimate contact with the intestinal wall. These movements have not a translatory effect, and a column of food may remain at the same level in the gut for a considerable time.

The *pendular movements* are less conspicuous, and appear as side-to-side swaying movements of individual loops of the intestine. They are probably a consequence of a to-and-fro movement of intestinal contents resulting from intermittent contractions in different parts of the loop (ALVAREZ).

The *peristaltic waves* cause onward progress of the contents of the intestine. The classical description of peristalsis is that given by Bayliss and Starling, who described it as a wave moving slowly—generally at about 2 cms. a minute—involving contraction of the gut above the food mass, and relaxation below it. If a balloon be inserted in the lumen of the exposed gut, it will be found that pinching the gut *above* the balloon causes an immediate relaxation of the muscular wall in the neighbourhood of the balloon. On the other hand, pinching the gut half an inch below the situation of the balloon causes a strong continued contraction to occur at the level of the balloon itself (Fig. 315). Stimulation at any portion of the gut causes contraction above the point stimulated and relaxation below it (the 'myenteric reflex'). The same effect is produced by introduction of a bolus of food, especially if it be large or

have a direct irritating effect on the wall of the gut (Fig. 316). In this case the contraction above and the inhibition below cause an onward movement of the bolus, which travels slowly down the whole length of the gut until it passes through the ileocæcal opening into the large intestine. According to Alvarez, the direction of the peristaltic wave is determined



FIG. 315. Intestinal Contractions (Balloon Method).

In this dog all the abdominal ganglia had been excised, and both vagi cut. Showing propagated effects of mechanical stimulation above and below the balloon. (1) pinch above, (2) pinch below, (3) pinch below balloon.

by the direction of the metabolic gradient of the intestine. The peristaltic contraction involves the co-operation of the local nervous system, viz. Auerbach's plexus. Whereas in the œsophagus it is the central nervous system which is involved, the peristaltic contractions in the small intestine

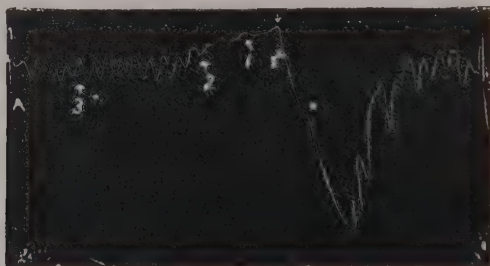


FIG. 316. Passage of Bolus. Contractions of Longitudinal Coat (Enterograph).

The bolus (of soap and cotton wool) was inserted into the intestine four inches above the recorded spot at A. The figures below the tracing indicate the distance of the middle of the bolus from the recording levers. As the bolus arrives two inches above the levers, there is cessation of the rhythmic contractions and inhibition of the tone of the muscle. This is followed, as the bolus is forced past, by a strong contraction in the rear of the bolus.

occur after severance of all connection with the brain and spinal cord. On the other hand, they are absolutely abolished by painting the intestine with nicotine or with cocaine.

According to Alvarez, the peristaltic wave, as described by Bayliss and Starling, is abnormal, and in his opinion true peristalsis consists of a series of 'rushes' traversing the whole length of the small intestine, travelling much more rapidly (2 to 25 cm. per second), and in which the constriction is less intense and not preceded by a wave of relaxation.

Anti-peristalsis is never observed in the lower small intestine. Mall

has shown that, if a short length of gut be cut out and reinserted in the opposite direction, a species of partial obstruction results, in consequence of the fact that the peristaltic waves, started above the zone of operation, cannot travel downwards over the reversed length of gut. The intestine above this level therefore becomes dilated. If, however, the reactions of the

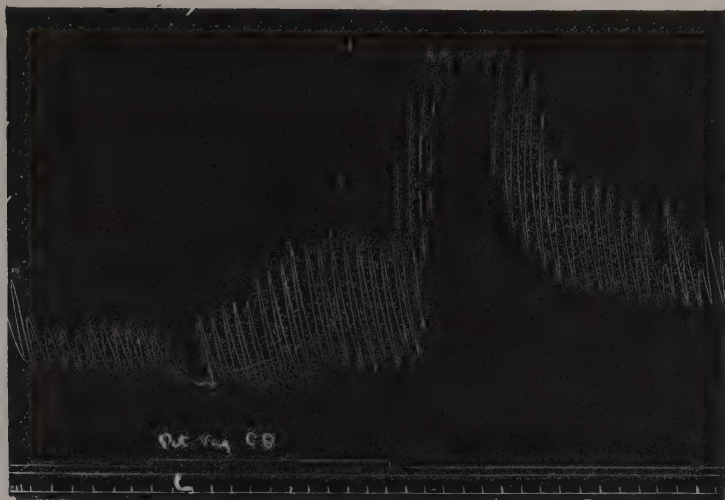


FIG. 317. Effect of Stimulation of Right Vagus on Intestinal Contractions.

local nervous system be paralysed or inhibited, a reflux of intestinal contents is quite possible, since the contractions excited at any spot by local stimulation of the muscle have the effect of driving the food either upwards or downwards; the direction of movement of the food will be that of least resistance.

The movements of the small intestine are also subject to the central

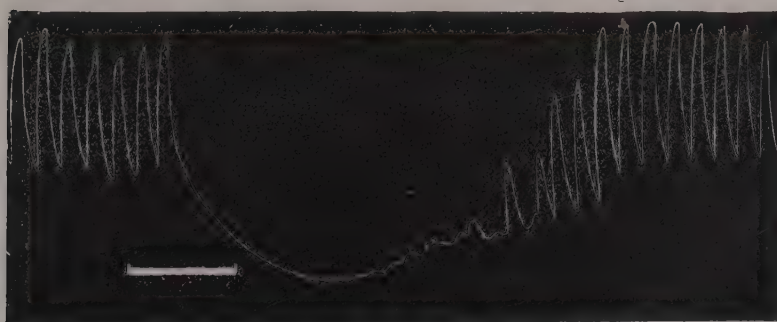


FIG. 318. Excitation of both Splanchnic Nerves. Balloon Method. Intestine returned to Abdomen.

nervous system. Stimulation of the vagus has the effect of producing an initial inhibition of the whole small intestine, followed by increased irritability and increased contractions (Fig. 317). On the other hand, stimulation of the splanchnic nerves causes complete relaxation of both coats of the small gut (Fig. 318). It seems that the splanchnics normally exercise a tonic inhibitory influence on the intestinal movements, which can be increased

reflexly by all manner of stimuli. On this account it is often impossible to obtain any movements in the exposed intestine so long as this remains in connection with the central nervous system through the splanchnic nerves. The relaxed condition of the gut which obtains in many abdominal affections is probably also similar in origin, and is due to reflex inhibition through the splanchnic nerves.

The movements of the duodenum show some special features, viz. contraction of the first part (duodenal cap), peristalsis of the second and third parts, antiperistalsis of the second and third parts, and segmenting movements. Normally the contents are passed to and fro a few times in the duodenum before passing on to the jejunum, but once they have passed on they do not return. Antiperistalsis is most definite in the second part of the duodenum, and leads to periodic filling of the duodenal cap, or even to regurgitation into the stomach. Very rapid mixing of the contents with the digestive juices results from this to-and-fro movement (BOLTON).

As a result of the intestinal movements described above, the food is thoroughly mixed with the digestive juices, and the products of digestion are brought into contact with the intestinal wall and absorbed. What is left—a proportion varying in different animals according to the nature of the food—is passed on by occasional peristaltic contractions through the lower end of the ileum into the colon or large intestine. The lowest 2 cm. of the ileum present a distinct thickening of the circular muscular coat, forming the ileocolic sphincter. This sphincter relaxes in front of a peristaltic wave and so allows the passage of food into the colon. On the other hand, it contracts as a rule against any regurgitation which might be caused by contractions in the colon. Although thus falling into line with the rest of the muscular coat as concerns its reaction to stimuli arising in the gut above or below, it presents a marked contrast to the rest of the gut in its relation to the central nervous system. It is unaffected by stimulation of the vagus. Stimulation of the splanchnic, however, which causes complete relaxation of the lower part of the ileum with the rest of the small intestine, produces a strong contraction of the muscle fibres forming the ileocolic sphincter (ELLIOTT). According to Hurst, an important function of the ileocolic sphincter is, by its tonic contraction, to prevent the contents of the ileum passing too rapidly into the cæcum, so as to allow more time for digestion and absorption of foodstuffs to be carried out in the ileum.

FUNCTIONS OF THE LARGE INTESTINE

Great differences are found in the structure of the large intestine of different animals, which depend entirely on the nature of their food. In the carnivora the large intestine is short and narrow and possesses little or no cæcum. In herbivora the large intestine is well developed, with sacculated walls, and the cæcum is very large. Man occupies a somewhat intermediate position between these two classes. The differences between the total length of the alimentary canal in various animals are largely determined by the varying development of the large intestine. Thus in the cat the intestine is three times the length of the animal, in the dog from four to six times, in man from seven to eight times, in the pig fourteen times, and in the sheep twenty-seven times. The great development of the large intestine in vegetable feeders is due to the fact that, in this class of food, all the nutritious material is enclosed in cells surrounded by cellulose walls. In order that the foodstuffs may be dissolved by the digestive juices, these cellulose walls must be disintegrated. In none of the higher vertebrates do we find any cellulose-

digesting enzyme, *cytase*, produced in the alimentary canal. The cellulose is dissolved either by the agency of bacteria or by means of cytases in the vegetable cells themselves. Thus in ruminants the masses of grass and hay are first received into the paunch, where they are kept warm and moist with saliva. Opportunity is thus given for the development of huge numbers of micro-organisms which can dissolve cellulose. From time to time portions of the sodden mass are returned to the mouth, chewed and then swallowed again to be subjected to the action of the proper digestive juices. In the horse and rabbit the chief part of the digestion of the cellulose occurs in the cæcum. Even after abstinence from food for some time the cæcum is still found to contain food material. In the cæcum, under the action of bacteria, the cellulose is dissolved and the cells are opened up so as to allow their contents to escape. The products of digestion of cellulose include a number of lower fatty acids, as well as methane, carbon dioxide and hydrogen. In the paunch the acids accumulate so that fermentation occurs in an acid medium, whereas in the cæcum the acids are neutralised by the secretion of alkali and the reaction remains practically neutral.

In carnivora the large intestine has very unimportant functions to discharge in digestion and absorption. The products of digestion are practically entirely absorbed by the time that the food has arrived at the ileocolic valve. In man the importance of the large intestine will vary with the nature of his food. If, however, a large quantity of vegetable food be taken, such as fruit or green vegetables, or cereals roughly prepared and coarsely ground, a considerable amount of material may reach the large intestine unabsorbed. A small proportion of this may undergo absorption in the large intestine, while the rest will pass out with the fæces, increasing their bulk.

A section of the mucous membrane shows a number of simple tubular glands. The greater number of the cells lining these glands are typical 'goblet' cells and contain plugs of mucin. Investigation by the fistula method shows that, when empty, the secretion of the large intestine is extremely scanty and composed wholly of mucus, while when stimulated mechanically by introduction of a drainage tube, a slight watery secretion is further contributed. The secretion of mucus not only aids the passage of the fæces along the gut, but probably impedes the propagation of the bacteria which are present in countless numbers in the fæces. This may account for the fact that, although bacteria are so numerous in the fæces most of them are dead. The mucous secretion of the large and small intestines together helps to hold the fæces together, and adds definitely to their bulk. The secretion of the large intestine is alkaline, which assists in the neutralisation of acids produced by bacterial fermentation. It contains erepsin, amylase and invertase.

As an absorbing organ the large intestine of man is of little importance. From observations on fistulæ in man it has been calculated that about 500 c.c. of water pass the ileocolic valve in the twenty-four hours. Of these about 400 c.c., together with the water secreted in the large intestine itself, undergo absorption in the large intestine. The absorption of any of the food substances by this part of the gut is much slower than that which takes place on introduction by the mouth. In some cases after the introduction of large enemata into the large intestine, a certain amount may escape backwards into the ileum and may there undergo absorption. The isolated large intestine of man is able to absorb only about 6 grammes of glucose per hour and about 80 c.c. of water. If egg albumin or caseinogen solutions be introduced by the rectum, no absorption can be detected after several hours. Feeding by nutrient enemata is thus of little value.

The chief value of the large intestine in carnivora and in civilised man would seem to be as an excretory organ, since it plays an important part in the excretion of calcium, magnesium, iron and phosphates. *Calcium* salts are excreted partly with the fæces, partly in the urine. If phosphates are present in large quantities, the greater part of the calcium will be excreted by the large intestine and escape with the fæces as insoluble calcium phosphate or as calcium soaps. If acids, such as hydrochloric acid, be administered, the amount of calcium in the urine will increase, and that in the fæces will diminish. Thus in herbivora normally only about 3 to 6 per cent. of the calcium is excreted in the urine, whereas in carnivora with an acid urine the proportion leaving the body by this channel rises to 27 per cent. The excretion of *magnesium* is determined by very similar conditions. Its phosphates are somewhat more soluble than those of calcium. In man about 50 per cent. of the magnesium leaving the body is contained in the urine, whereas the amount of calcium in the fæces is ten to twenty times as much as that contained in the urine. It must be remembered that the whole of this difference is not due to actual excretion of calcium into the gut, since a certain proportion of it may be precipitated as an insoluble phosphate or carbonate in the upper part of the small intestine and pass through the gut without undergoing absorption.

The absorption of *iron* takes place in the duodenum and upper part of the jejunum. Only 1 or 2 milligrammes appear in the urine, all the rest being excreted in the large gut and appearing in the fæces, chiefly as sulphide of iron.

Of the acid radicals, *phosphates* may pass out either with the urine or with the fæces, the exact path taken being determined by the relative amount of calcium and alkaline metals present in the food. If there is an excess of calcium most of the phosphates will leave with the fæces.

The large intestine is the main channel of excretion for certain substances, *e.g.* the heavy metals, such as bismuth and mercury. If bismuth be administered subcutaneously, the fæces will be found to contain this substance, and the wall of the large intestine will be stained black from a deposit of sulphide of bismuth. This deposit stops short at the ileocolic valve.

MOVEMENTS OF THE LARGE INTESTINE. By means of the occasional peristaltic contractions, accompanied by relaxation of the ileocolic sphincter, the contents of the small intestine are gradually transferred into the colon. When food is swallowed, or when chyme enters the duodenum, a peristaltic rush is initiated in the small intestine; on the arrival of the wave at the ileocæcal valve, the sphincter opens and allows the passage of some of the contents of the ileum into the colon ('gastro-ileal' reflex). In man the contents are considerable in bulk, are semifluid, and probably fill the ascending as well as the transverse colon.

The large intestine is supplied with nerves from the central nervous system. These run partly in the sympathetic system along the colonic and inferior mesenteric nerves, partly in the pelvic visceral nerves or *nervi erigentes*, which come off from the sacral cord and pass direct to the pelvic viscera. In addition it possesses a local nervous system, presenting the same structure as that found in the small intestine. The movements of the large intestine differ considerably in various animals, as has been shown by Elliott, according to the nature of the food and the part played by this portion of the gut in the processes of absorption. In the dog, absorption is almost complete at the ileocolic valve, whereas in the herbivora a very large part of the processes of digestion and absorption occurs in the colon and

cæcum. Man takes an intermediate position between these two groups of animals as regards his large intestine.

The movements of the large intestine in the cat may be observed by the X-ray method. The food as it passes from the ileum first fills up the proximal colon. The effect of this distension is to cause a contraction of the muscular wall at the junction between the ascending and transverse colon. This contraction travels slowly over the tube in a backward direction towards the cæcum, and is quickly succeeded by another, so that the colon may present at the same time several of these waves. These waves are spoken of as anti-peristaltic; but as they do not involve also an advancing wave of inhibition, they must not be regarded as representing the exact antithesis of a peristaltic wave, as we have defined it. The effect of these waves is to force the food into the cæcum, regurgitation into the ileum being prevented partly by the obliquity of the opening, partly by the tonic contraction of the ileocolic sphincter. As the whole of the contents cannot escape into the cæcum, a certain portion will slip back in the axis of the tube, so that these movements cause a thorough churning up of the contents and their close contact with the intestinal wall. The movements are rendered still more effective by the sacculation of the walls. The distension of the cæcum caused by this anti-peristalsis excites occasionally a true co-ordinated peristaltic wave which, starting in the cæcum, drives the food before it into the transverse colon. These waves die away before they reach the end of the colon, and the food is driven back again by waves of anti-peristalsis. Occasionally more food escapes through the ileocolic sphincter from the ileum, so that the whole ascending and transverse colon may be filled with the mass undergoing a constant kneading and mixing process. The result of this process is the absorption of the greater part of the water of the intestinal contents, as well as of any nutrient material; and the drier part of the intestinal mass collects towards the splenic flexure, where it may be separated by transverse waves of constriction from the more fluid parts which are being driven to and fro in the proximal and intermediate portions. By means of occasional peristaltic waves these hard masses are driven into the distal part of the colon.

In man the movements of anti-peristalsis are much more feeble than in the cat, and as a rule cannot be observed in X-ray examination. Indeed the cæcum and ascending colon seem to be quite passive, their filling being effected by the peristaltic contractions of the ileum. About 350 grammes of fluid chyme per day pass the ileocæcal valve; water and a little nutrient material is absorbed, chiefly in the cæcum and ascending colon, though the contents remain soft till they reach the pelvic colon, when they undergo inspissation, so that the average weight of fæces per day is about 135 grammes.

After an average meal the colon begins to fill in about two hours, and the ileum is empty after about six and a half hours, though there is great variation amongst individuals. The time taken for a bismuth meal to reach various levels in the colon in man is shown in the accompanying figure (Fig. 319). It should be remembered, however, that a bismuth meal is usually given after previously emptying the whole alimentary canal as completely as possible. In the normal course of events food residues are much slower in being completely eliminated in the fæces than these figures would indicate. Thus Alvarez and Freedlander, administering coloured glass beads with the food to normal adults, found that, even after four days, only about three-quarters of the beads had been recovered.

A distinguishing feature of the distal colon is its complete subordination to the spinal centres. It probably remains inactive until an increasing

distension excites reflexly through the pelvic visceral nerves a complete evacuation of this portion of the gut. Stimulation of these nerves in an animal, such as the cat, produces a rapid shortening of the distal part of the colon, due to contraction of the recto-coccygeus and longitudinal fibres of the gut, followed after some seconds by a contraction of the circular coat. This originates certainly as high as the splenic flexure, and possibly even higher, and spreading rapidly downwards empties the whole of this segment of the gut. In man the emptying of the rectum itself is largely assisted by the

contractions of the voluntary muscles of the abdominal walls and pelvic floor. 'Mass contractions' of the colon may occur as a reflex result of taking food into the stomach. Hence the act of defæcation after breakfast, or in patients with irritable intestines after any meal. The last section of the rectum is emptied at the close of the act by a forcible contraction of the levator ani and the other perinæal muscles, and this contraction also serves to restore the everted mucous membrane.

The carrying out of this reflex act is dependent on the integrity of a certain part of the lumbar spinal cord. If this 'centre' be destroyed, the tonic contraction of the sphincter muscles disappears. This centre may either be excited to increased action, or be inhibited by peripheral stimulation of various nerves, or by emotions such as fear. Application of

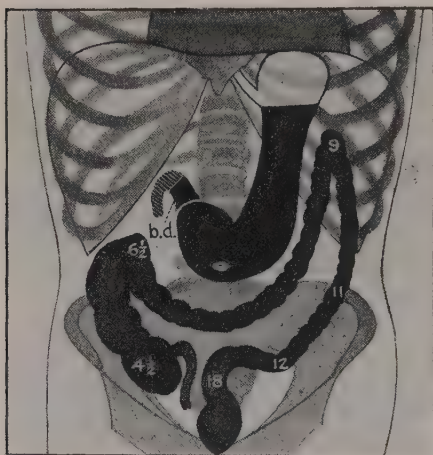


FIG. 319. Skiagram to show Normal Position of Colon in Man, and the Position attained by its Contents at different periods after a Meal containing Bismuth.

The times of arrival at different levels are marked on the colon and are measured in hours after the meal. (HURST.)

warmth to the region of the anus causes reflex relaxation of the sphincter; application of cold increases its tonic contraction.

In man, as Hurst has shown by the skiagraphic method, the pelvic colon becomes filled with fæces from below upwards, the rectum remaining empty till just before defæcation. In individuals whose bowels are opened regularly, the entry of fæces into the rectum gives rise to a sensation of fulness and acts as the call to defæcation. If no response be made, the desire to defæcate passes away, since the rectum relaxes and the fæcal mass no longer exercises pressure on its wall. Hurst has shown that the minimal pressure required to produce the call to defæcate varies from 30 to 40 mm. Hg, according to the length of the gut which is the seat of distension.

THE FÆCES

In man or the carnivora the absorption of the constituents of a meal, whether consisting of fats, proteins or carbohydrates, is practically complete by the time that the food has arrived at the lower end of the ileum. The fæces in the main are not derived from the food, but are produced almost entirely in the alimentary canal itself. This is shown by the fact that on analysing the fæces no soluble carbohydrates or proteins, albumoses, pep-

tones or amino-acids are to be found. After a meal of meat, microscopic examination of the fæces reveals no trace of striated muscle fibres. Moreover, animals in a state of complete starvation form fæces which do not differ in their composition from the fæces which are found after feeding with meat, eggs, sugar or cooked starch, though the amount is less in a state of inanition than under normal circumstances. In one experiment Hermann isolated a loop of gut, joining its ends together so that a continuous ring was formed. The continuity of the gut was then restored by suturing the two free ends. After some weeks the isolated loop was found to contain a semi-solid material similar to fæces in appearance, consistence and chemical composition. It contained a large amount of phosphoric acid, lime and iron.

So long as vegetables or coarsely ground cereals are excluded from the diet, the nature of the latter does not alter the chemical constitution or appearance of the fæces. Under these circumstances the fæces have the following composition :

Water	.	.	.	.	.	65 to 67 per cent.
Nitrogen	.	.	.	.	.	5 to 9 "
Ether extract	.	.	.	.	.	12 to 18 "
Ash	.	.	.	.	.	11 to 22 "

The ash consists chiefly of lime and phosphoric acid with some iron and magnesia. The ethereal extract contains fatty acids and a small amount of lecithin. Neutral fat is present in very small proportions. The fæces also contain small quantities of cholalic acid and its decomposition product, dyslysin, also coprosterol, a reduction product of cholesterol, and a certain amount of purine bases, consisting of guanine, adenine, xanthine and hypoxanthine. On the average the fæces contain about 0.11 gramme of purine bases per diem, about seven times as much as is contained in the urine passed in the same time. The material basis of the fæces seems to be largely inspissated mucus, bile and other secretions, desquamated epithelial cells from the intestinal wall, and bacteria, of which countless numbers, chiefly dead, are present. It has been reckoned that as much as 50 per cent. by weight of the fæces may consist of dead bacteria.

Very different is the composition of fæces if the food contains a large amount of cellulose. Not only does the ingested cellulose pass unchanged into the fæces, but large quantities of other substances enclosed in the cellulose walls may also escape digestion and absorption. Moreover the increased bulk of the undigested residue stimulates peristalsis, and thus quickens the passage of the food through the gut to such an extent that the digestive juices may not have time to exert their full action on the food. The influence of the character of the food is well illustrated by a comparison of the amount and composition of the fæces on different kinds of bread (RUBNER) :

Kind of bread.	Weight of moist fæces.	Weight of dried fæces.	Percentage of ingested food.	Nitrogen (grms.).
Bread from fine flour .	132.7	24.8	4.03	2.17
Bread from coarse flour .	252.8	40.8	6.66	3.24
Brown bread . . .	317.8	75.79	12.23	3.80

The indigestible cellulose in the food is not without value. It has been shown previously that the peristaltic contractions of the intestine are roused primarily by the mechanical stimulus of distension. If the food is capable

of entire digestion and absorption, the amount of fæces formed is limited to that produced by the intestinal wall itself. The small bulk exercises very little stimulating effect on the intestine, and the movements of the latter will therefore tend to be sluggish, especially in the absence of the mechanical stimulus determined by muscular exercise. The presence of a certain amount of cellulose in the diet may therefore be of considerable advantage by giving bulk to the fæces and ensuring the proper regular evacuation of the lower gut. It is probable that the constipation which is so common a disorder in civilised communities is due as much to the refinement in the preparation of the food as to the prevalence of sedentary occupations incident on the working of such communities.

CHAPTER XXIX

THE ABSORPTION OF THE FOODSTUFFS

THE ABSORPTION OF WATER AND SALTS

THE intake of water, and probably of salts, into the body, in accordance with the requirements of the organism as a whole, seems to be regulated almost entirely by the central nervous system, the higher parts of this system, viz. those concerned with appetite, being particularly involved in the process. Thus in man any large loss of fluid to the body, as by sweating, diarrhœa, or hæmorrhage, gives rise to an intense thirst that has its natural reaction in increased intake of water by the mouth. On the other hand, the property possessed by the alimentary canal of absorbing water and weak saline fluids contained in its interior is very little influenced by the state of depletion, or otherwise, of the water depôts of the body. It is practically impossible, however large the quantities of fluid ingested, to evoke the production of fluid motions, the greater part of the ingested fluid being absorbed on its way through the alimentary canal. Thus a man may keep himself in perfect health and maintain the water balance of his body steady, whether he take one litre or six litres of water daily. The whole process of regulation, apart from that determined by appetite, is carried out at the other end of the cycle, viz. by the kidneys.

The absorption of water in the stomach may be regarded as nil. Although from this viscus alcohol and some dissolved substances, *e.g.* sugar, may be absorbed to a slight extent, water or saline fluids introduced into it are passed through the pylorus, either without change, or increased by the secretion of fluid from the gastric glands. The chief absorption of water occurs in the small intestine. It is on this account that the salient features of cases of dilatation of the stomach with stenosis, absolute or relative, of the pyloric orifice can be nearly all referred to the starvation of the body in water, and can be often relieved by the administration of water, either subcutaneously or by the rectum, *i.e.* by the channels through which absorption is still possible. Water that has been swallowed to quench thirst, has first to be passed from the stomach into the small intestine before it can be absorbed and relieve the needs of the tissues. The intestinal contents at the ileocæcal valve contain relatively nearly as much water as they do at the upper part of the jejunum. Their absolute bulk, however, is much smaller, so that only a small proportion of the water that has been taken in by the mouth remains to be absorbed in the large gut—an amount probably much less than that which has been added to the contents of the small intestine in the form of secretions by the stomach, liver, pancreas and intestinal tubules.

The absorption of water and saline fluids is greatly facilitated by the presence of the villi of the small intestine. By means of these structures the absorbing surface of the intestine is largely increased. It has been calculated that each square millimetre of intestine represents an absorbing surface of 3 to 18 mm.², and a total capillary surface of about the same order, though

not all these capillary surfaces are superficial in position. Each villus (Fig. 320) consists of a framework of reticular tissue containing many leucocytes in its meshes, separated from the lumen of the gut by a continuous layer of columnar epithelial and goblet cells. These cells rest on an incomplete basement membrane and present on the side turned towards the lumen of the gut a striated border.

The villus offers two channels by means of which material which has passed through its epithelium may be carried into the general circulation. In the middle of the villus is the central lacteal, a club-shaped vessel bounded by a complete layer of delicate endothelial cells. This leads into a plexus of lymphatics placed superficially to the *muscularis mucosæ*. From the superficial plexus communicating branches pass vertically to a corresponding plexus lying in the submucosa. The central lacteal and the superficial plexus are free from valves, which however are present in abundance

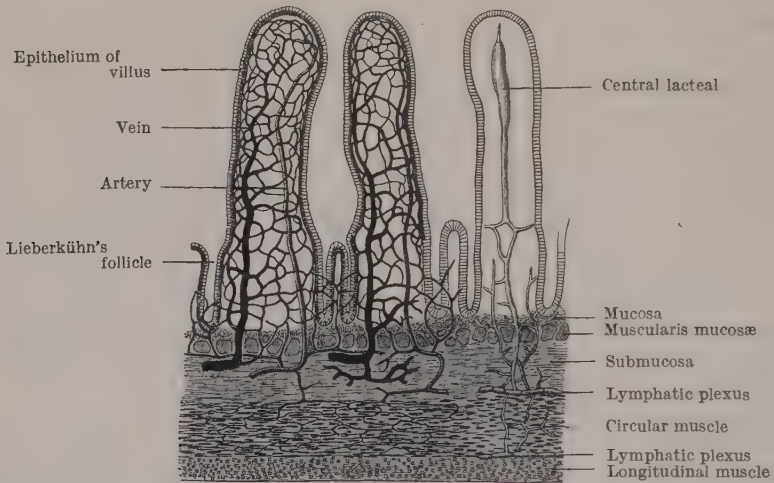


FIG. 320. Diagrammatic Section through Wall of small Intestine to show Vascular and Lymphatic Arrangements of Mucous Membrane. (After MALL.)

in the deeper plexus, so that fluid can pass easily from the lacteal to the deeper plexus, but not in the reverse direction. From the muscularis mucosæ, unstriated muscle fibres pass up through the villus, to be attached partly to the outer surface of the central lacteal, partly by expanded extremities to the basement membrane covering the surface of the villus. Contraction of these muscle fibres will tend to empty the central lacteal into the deep plexus of lymphatics and may also cause an expulsion of the contents of the spaces of the retiform tissue of the villus into the central lacteal. The alimentary canal represents one of the few localities where a formation of lymph is constantly proceeding, even in a condition of complete rest. On placing a cannula in the thoracic duct of a dog, an outflow of lymph is obtained which may vary in different animals between 1 c.c. and 10 c.c. in the ten minutes. The greater part of this lymph is derived from the alimentary canal, so that any of the intestinal contents which have made their way into the spaces of the villus might be entrained in this lymph current and carried away with it into the thoracic duct and so into the general blood system.

The other possible channel of absorption is by the capillary blood

vessels of the villus. Each villus is supplied with blood from one or two arterioles which break up into a rich plexus of capillaries lying close under the basement membrane of the villus. The total surface area of the portions of the outer capillary walls which lie immediately below the epithelium, is about one-third of the whole epithelial surface, so that the surface through which interchange may occur between the contents of the bowel and the blood is roughly three to five times the area of the intestinal mucosa in plan. The return blood is collected into one or two veins, which join the radicles of the portal vein in the submucosa and in the mesentery. In these capillaries the blood is circulating rapidly, so that a considerable amount of material may pass into them from the spaces of the villus without appreciably altering the percentage composition of the blood. But it must be remembered that the blood in these vessels is at a high pressure, probably not less than 30 mm. Hg, so that we shall have to place out of court any possibility of the passage occurring in consequence of hydrostatic differences of pressure, *i.e.* by a process of filtration.

When salt solutions are introduced into the small intestine, they are rapidly absorbed without the production of any corresponding increase in the rate of lymph flow from the thoracic duct. On the other hand, the absorption of large amounts of fluid may cause an actual diminution of the solids of the plasma, so that we are justified in regarding the capillary network of blood vessels at the surface of the villi as solely responsible for the absorption.

What are the forces which cause this transference of fluid and dissolved substances from one side to the other of the membrane composed of epithelial cells *plus* capillary endothelium? Like other cells, those of the intestinal epithelium are bounded on their free surface by a 'lipoid' membrane, *i.e.* one containing some complex of lecithin and cholesterol, and permeable only to such substances as are soluble in lipoids. On the other hand, the cement substance between the cells may be of a different character and possibly permeable to water-soluble substances. The question has been propounded whether the greater part of the substances which enter the blood plasma from the gut pass between the cells or through the cells. Water could of course pass in either way. Most of the inorganic salts such as sodium chloride, as well as the very important constituents of the food, the sugars, are insoluble in lipoids and would have to pass between the cells. When the question is investigated by the use of dyestuffs, soluble or insoluble in lipoids, it is found that the lipoid-soluble dyestuffs, such as neutral red or toluidin blue, pass into the cells, whereas the dyestuffs which are insoluble in such substances pass into the intercellular spaces. Too much stress, however, must not be laid on these experiments; the fact that absorption of these dyestuffs is determined by the physical conditions of the cell membrane is no proof that the absorption of the normal food constituents is determined in the same way. In fact it is quite legitimate to assume that the lipid membrane or limiting layer round every cell has as its main office, not only the regulation of the access of foodstuffs to the cell, but its protection from any foodstuffs which it does not require for its metabolism. If it were not for such a membrane the assimilation of a salt would be determined entirely by its concentration in the immediate surroundings of the cell, whereas we know that assimilation by any living organism, whether uni- or multi-cellular, is regulated in the first place by the activity of the organism itself.

It seems more probable that the absorption of the different foodstuffs is effected by the cells themselves in accordance with their nutritional

needs; and this view is strengthened when we come to examine the absorption even of saline solutions. If 50 c.c. of normal sodium chloride solution be introduced into a loop of intestine, it is absorbed steadily, so that at the end of an hour not more than about 20 c.c. may be recoverable. The absorption of such a solution could be ascribed to the osmotic pressure of the colloids in the blood plasma or lymph within the spaces of the villi. If hypertonic solutions are employed, *e.g.* a 2 or 3 per cent. NaCl solution, salt is absorbed more rapidly than water; indeed there may for a time be an actual increase of the fluid contained in the gut. Here again we might ascribe the absorption of salt, and the dilution with water, to the physical factors diffusion and osmosis respectively. With hypotonic solutions, on the other hand, water is absorbed more rapidly than salt. If distilled water is introduced, there is passage of chloride into it from the blood until about 0.16 per cent. NaCl is reached; if this outward passage of chloride is to be attributed to reversible permeability of the membrane, it seems clear that this is limited.

When sugar solutions are employed, they behave in somewhat similar fashion to sodium chloride solutions, provided that the sugar is one of the absorbable hexoses, both sugar and water being rapidly absorbed. It is important to note that glucose is absorbed from the gut almost as rapidly as sodium chloride, and quite as rapidly as sodium iodide, although its diffusibility is very considerably less than either of these salts. Moreover, great differences, which are not referable to the diffusibility of the sugars in question, are found between the rates at which various sugars are absorbed. Thus glucose is absorbed most rapidly, fructose half as quickly, and mannose at about one-fifth the rate (CORI). There is never, under normal conditions, any passage of glucose outward from blood to bowel contents. The monosaccharides are absorbed much more rapidly than disaccharides; and it seems that, in the absence of hydrolytic splitting of the disaccharides, absorption of these substances from the gut would be entirely abolished. Lactose disappears from the intestine much more slowly than either of the other two disaccharides, so that large doses may have a laxative effect. In animals devoid of lactase in their intestinal epithelium, milk sugar is apparently not absorbed at all.

The most cogent argument in favour of an active intervention of the cells of the gut in the process of absorption is perhaps furnished by the study of the absorption of blood serum. It has been shown that if an animal's own serum be introduced into a loop of its intestine the serum undergoes absorption. This absorption affects the water and salts more than the protein, so that the percentage of the proteins in the fluid remaining in the intestine is increased. Finally, however, the whole of the serum is absorbed. In this case the fluid within the gut is identical with the fluid within the blood vessels. There are no differences in concentration, quality of salts, or osmotic pressure of proteins. Nevertheless water passes through the cells of the gut from their inner to their outer sides, entraining with it the salts of the serum and a certain proportion of the indiffusible proteins. It is impossible to explain this result as due to the digestion of the proteins and their conversion into diffusible products, since the intestinal loops were washed free of any trypsin that they contained, and serum has itself a strong antitryptic action which would prevent its being attacked by a solution of trypsin. It has also been claimed by Mills that tissue fibrinogens can be absorbed from the intestine and recovered unchanged from the urine.

The active intervention of the cells in the absorption of salt solutions and serum can be abolished by any means which diminishes or destroys their vitality, such as the addition of sodium fluoride to the fluid to be absorbed, or destruction of the epithelium by previous temporary occlusion of the blood vessels supplying the loop of intestine.

We must conclude that, when a fluid is introduced into the intestine, an active transference of water and solutes from the lumen into the blood stream is effected by the intermediation of forces having their origin in the metabolism of the cells themselves. This work of absorption of the cells may be aided or hindered according to the physical conditions present, though our knowledge of these physical conditions is at present too fragmentary to enable us to appraise the respective parts played on the one hand by the physical conditions and on the other hand by the activity of the cells, which primarily results from and secondarily modifies them by introducing fresh ones. If these act against the cells, *e.g.* if the fluid be hypertonic, the absorption is effected more slowly, while with hypotonic solutions the physical conditions concur with the vital activity of the cells in bringing about a very rapid transference of fluid from the gut into the blood vessels. Among these physical conditions we must reckon the nature of the salts present in the solution. If these can pass easily into, and through, the cells, *e.g.* ammonium salts, sodium chloride, absorption is carried out rapidly. If, on the other hand, the salts in the intestinal contents are but slightly diffusible, or have very little power of penetrating into the cells, the absorption of water by the cells causes an increased concentration of the salts, and therefore an increased osmotic pressure which offers a resistance to any further absorption; and the process comes to an end when the absorptive power of the cells is exactly balanced by the increased osmotic pressure, or attraction for water, of the intestinal contents.

Cushny and Wallace, as the result of their experiments on the relative absorbability of various sodium salt solutions from the gut, divide the salts into four main classes as follows:

I	II	III	IV
Sodium chloride, bromide, iodide, formate, acetate, propionate, butyrate, valerianate, caprate.	Ethyl sulphate; nitrate, lactate, salicylate, phthalate.	Sulphate, phosphate, ferrocyanide, caprylate, malonate, succinate, malate, citrate, tartrate.	Oxalate, fluoride.

Of these the first class contains those salts which are absorbed with great ease from the intestine. The second group of salts are absorbed with somewhat greater difficulty. The third group are absorbed so slowly, *i.e.* the salts retain the water in which they are dissolved so long, that they increase peristalsis and act as laxatives or purgatives. The members of the fourth class are not absorbed at all. It is evident that this classification is independent of the diffusibility of the salts. Sodium acetate has a much smaller dissociation value and a lower diffusibility than sodium chloride or iodide, and yet is absorbed at approximately the same rate as these two salts. There is, however, one character which apparently determines the non-absorbability (relative or absolute) of the members of the third and fourth classes. All these salts form insoluble compounds with calcium. This common character is not an explanation of the permeability of the cell wall, but is simply a general statement of one of the conditions which affect the power of the cells to take up salts from their solutions, this power being absent in the case of salts which furnish an insoluble calcium compound.

Other physical factors which no doubt exert an influence, though to an unknown extent, are electro-osmosis, Donnan equilibria, imbibition and surface action.

THE ABSORPTION OF FATS

The problem of fat absorption is ultimately one of the transference of the neutral fat of the food to the circulating fluids in such a form that it can be carried by them to the place where it is required.

The processes of digestion of fat result in the production of glycerol and fatty acids, if the reaction be neutral or slightly acid. If the reaction of the

gut be alkaline, the alkali will combine with the fatty acids to produce soaps. Analyses of the contents of the gut after a fatty meal show that the greater proportion of the fats are present as a mixture of fatty acids and soaps, the amount of these substances as compared with unchanged fat increasing as we descend the gut.

In studying the absorption of fat the investigator is able to take advantage of the fact that fats or fatty acids containing unsaturated fatty acids have the property of reducing osmic acid, and therefore of being stained black by this reagent. Practically all the fats which occur in the food or in the cells of the body contain unsaturated as well as saturated fatty acids, and therefore give this reaction. In many cases it is useful to employ the specific stains for fats, such as Sudan red or alkanna red. It is important to remember that the intensity of the fat reaction given by a cell is only an expression of the fat or fatty acid contained in a free state in the cell, and is no criterion of the total amount of fat which may be present. Thus a normal heart muscle in section gives only a diffuse light brown coloration with osmic acid. After poisoning by phosphorus or by diphtheria toxin, every muscle cell may be found studded with minute black granules of fat. Chemical analysis shows, however, that the normal heart muscle contains as much fat as the degenerated muscle. Our micro-chemical methods will therefore throw no light on the amount of fat which is actually in combination with the cell protoplasm.

If an animal be examined a few hours after the administration of a meal rich in fats, the lymphatics of the intestine are seen to be distended with a milky fluid—*chyle*—and the same fluid is found filling the *cisterna lymphatica magna* and the thoracic duct. The opacity is due to the presence of minute granules of neutral fat. Some of these, called *chylomicrons*, are extremely minute (0.5 to 1 μ). The fat in such chyle may amount to over 6 per cent., so that in a moderate-sized dog 12 grammes of fat may be carried in the course of an hour from the intestine to the blood by this means. This great access of fat to the blood during fat absorption introduces corresponding changes in the blood, and chylomicrons appear in the blood in half to one and a half hours. The plasma itself becomes milky (lipæmic), and if the blood be allowed to clot, the serum expressed from the clot is also milky. On standing, a layer of fat globules may rise like cream to the surface of the serum. Fat is found in a free state in this finely divided condition in the blood plasma so long as it is being absorbed from the intestine. In from six to ten hours after absorption is complete it disappears entirely, the serum becoming perfectly clear. Thus part at any rate of the fat which is absorbed from the gut is carried thence by the lymphatic channels in the form of neutral fat to the blood stream, by which it is distributed to the various tissues of the body, gradually leaving the blood stream in a manner which at present has not been determined. Not all the fat which is absorbed takes this path by way of the lymphatics and the thoracic duct. Ligature of the thoracic duct, if effective, certainly impedes the absorption of fat, but does not abolish it. If the thoracic duct lymph be collected during the absorption of a given quantity of fat from the intestine, not more than 60 per cent. of the fat which has disappeared from the gut can be recovered from the lymph. What happens to the remainder we do not know. If the thoracic duct be ligatured, the percentage of fat in the blood rapidly falls to a minimum which remains constant, even during starvation. If now fat be administered, although a considerable proportion of it may be absorbed, the percentage of fat in the blood is not raised. If, therefore, the fat is absorbed directly into the blood, it cannot be in the particulate condition, and it must be in such small quantities at a time that it is at once removed from the blood by the tissues.

Microscopic examination of a section of a villus during fat absorption shows that the absorption occurs for the most part through the epithelial

cells. These are found closely packed with fat granules (Fig. 321) which, small at the beginning of the process of absorption, rapidly enlarge till they occupy the greater part of the cell lying between the nucleus and the basilar striated border. Most observers are agreed that no fat globules are to be seen within the border itself.

According to Altmann, the fat granules found in the cells during absorption are themselves produced by a transformation of fuchsinophile granules which are present in the cell even during the fasting condition. At an early stage the small fat granules can be stained so as to show a distinct fuchsinophile envelope. Altmann interprets this appearance as showing that the epithelial cells take up the fat in a dissolved form, probably in a hydrolysed condition, and that a process of synthesis then occurs in the granules, leading to the formation and accumulation of fat. When the process of absorption is proceeding actively, the meshes of the villus contain a number of free fat granules, and the leucocytes in these meshes are also generally found full of these granules. According to Schafer an important function in the transfer of the granules from epithelial cells to central lacteal was performed by the leucocytes. These were supposed to take up the fat granules extruded by the epithelial cells at the base of the villi, to wander into

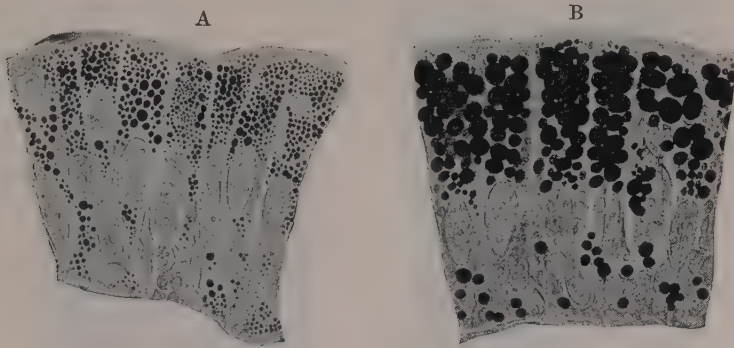


FIG. 321. Columnar Epithelium from small Intestine of Frog stained with Osmic Acid to show Fat Absorption.

A. Five hours after a meal of olive oil. B. Three hours later. It should be noticed that the fat globules first formed grow in size in the course of digestion, pointing to a gradual deposition of fat on the globules from solution in the protoplasm. (SCHAFFER.)

the central lacteal, where they broke down, furnishing in this way the molecular basis of the chyle as well as its protein constituents. This view was strongly combated by Heidenhain, who pointed out that many of the granules staining darkly with osmic acid were not necessarily fat, and that the number of leucocytes within the villi were hardly sufficient to account for the amount of material observed. According to Reuter the epithelial cells take up fat in a dissolved condition through the striated border, and deposit it as granules of neutral fat in the inner portion of the protoplasm. From here the fat is passed on by the protoplasm by the side of the nucleus and extruded in the form of very fine granules in the deeper parts of the inter-epithelial clefts, which thus function as true excretory channels for the epithelial cells (Fig. 322).

It is probable that the contraction of the villi, described many years ago by Brücke, plays an important part in the absorption of fats. On opening the gut under warm saline solution, the villi can be seen under the microscope to contract to about half their length, and lengthen rhythmically, and to present at the same time a waving movement. Repeated contractions of the muscle fibres of the villus would tend to empty the spaces into the central lacteal, and this in its turn into the sub-mucous plexus of lymphatics, so that the lymph in the spaces is constantly renewed and passes, laden with absorbed fat particles, into the valved lymphatics of the mesentery. The villi contract in response to various

mechanical and chemical stimuli, *e.g.* pressure in the central lacteal, bile salts, &c.

It was long considered that the fats were taken up by the epithelial cells of the intestine as very fine particles of neutral fat, the chief use of the pancreatic juice being to produce enough soap to aid the formation of an emulsion of fat in the intestines. Recent work by J. Mellanby suggests that this view may, after all, be worthy of consideration, since he finds that, in presence of bile, an emulsion of neutral fat is readily absorbed without any evidence of preliminary saponification. There is also evidence that, when saponification has occurred, the fats are absorbed, *dissolved* in the bile, either as soap or as fatty acid. The arguments for this view can be shortly summarised as follows :

(1) Although the bile does not dissolve neutral fats, it has a strong solvent action on fatty acids, on soaps, and even on the insoluble calcium soaps.

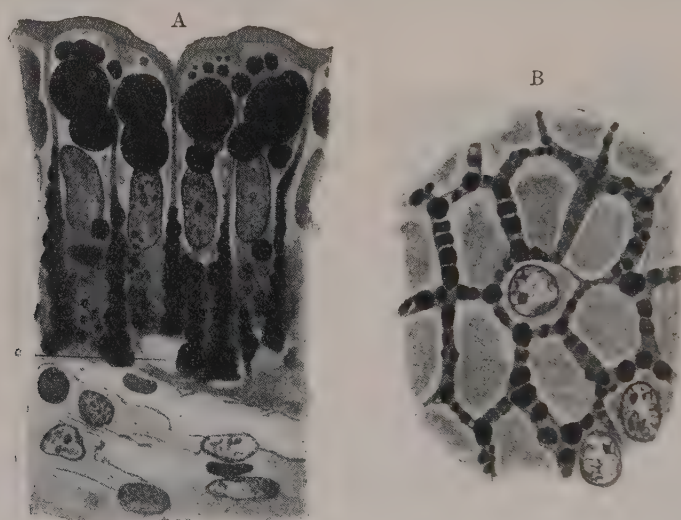


FIG. 322. A. Vertical section through Intestinal Epithelium of a Rat during Fat Absorption.

B. Horizontal section through deeper parts of the Cells, showing presence of fine fat Globules into the intercellular Clefts. (REUTER.)

This solvent power is greatest in the case of oleic acid, of which bile can dissolve 19 per cent. It is very small in the case of pure stearic acid, but the solubility of the latter acid is largely increased if it be associated, as is usual, with oleic acid. Moore has shown that this solvent action is chiefly conditioned by the bile salts, aided by the lecithin and cholesterol also present in the bile, a solution of lecithin and cholesterol in bile salts having a greater solvent power than the salts alone.

(2) The presence of bile in the intestine is essential for the normal absorption of fat. If the bile be cut off by occlusion of the bile ducts or by the establishment of a biliary fistula, the utilisation of fat sinks from about 98 per cent. to about 40 per cent., the unabsorbed fat appearing in the faeces. This large undigested residue of fat also hinders the absorption of the other foodstuffs by covering them with an insoluble layer, so that nutrition as a whole may suffer considerably.

(3) Absorption may also be interfered with by ligature of the pancreatic

duct. This result is probably due to the absence from the intestine of the fat-splitting enzymes of the pancreatic juice. If the fæces be analysed, it is found that a very large proportion of the fat has been split into fatty acids in the course of its passage through the alimentary canal. This lipolysis has, however, been carried out by the agency of micro-organisms, *i.e.* in the lower segments of the gut where the greater part of the bile has been already reabsorbed into the portal circulation. If fat, in a finely divided form such as cream or milk, be given to animals deprived of their pancreas, a certain proportion of it is absorbed. Under these conditions some lipolysis may occur in the stomach itself.

(4) It was shown by Schiff, by means of his amphibolic fistula, that the bile which is poured into the gut undergoes a circulation, being re-absorbed from the lower parts of the digestive tube, carried to the liver by the portal vein, and re-secreted in the bile. The same quantity of bile salts may therefore be used over and over again.

(5) Substances which are physically almost identical with fats, *e.g.* petroleum or paraffin, are not absorbed even when introduced into the intestine in the finest possible emulsion. If neutral fat be melted with a soft paraffin and the resulting mixture made into a fine emulsion and administered, it is found that the intestine rejects the paraffin, but takes up the neutral fat. This result can be explained only by assuming that the fat in the particles has been actually dissolved out by the digestive juices and has been absorbed in a state of solution.

Under normal circumstances the utilisation of fat is almost complete. By the time the intestinal contents have arrived at the lower end of the ileum, 95 per cent. of the fat has been absorbed. Removal of the whole large intestine was found by Vaughan Harley not to affect fat absorption in the dog.

THE ABSORPTION OF CARBOHYDRATES

As a result of the action of the various digestive juices, all the carbohydrate constituents of the normal diet of man are reduced to monosaccharides. The absorption of these digestive products may take place in any part of the alimentary canal, the greatest part in the act of absorption being played by the small intestine. By the time that the food has arrived at the ileocaecal valve, practically the whole of the carbohydrate constituents of the food have been absorbed. All experimenters are agreed that the carbohydrates pass into the body by way of the vessels of the portal system. The lymph from the thoracic duct contains no more sugar than does the arterial blood taken at the same time, whereas there is an increased percentage of sugar in the portal blood, and even in the general circulation, during the absorption of a big carbohydrate meal.

Of the carbohydrates of the food, some, like starch, dextrin, glycogen, are colloidal and indiffusible; others, such as the disaccharides, cane sugar, milk sugar and maltose, are soluble and diffusible; and the products of the action of digestive enzymes on these two classes, namely the monosaccharides, mannose, fructose, glucose and galactose, are also soluble and diffusible. The problem as to the mechanism involved in the passage of these substances across the intestinal wall into the blood vessels has been already dealt with in treating of the absorption of water and salts. The most striking fact is the relative impermeability of the intestinal wall to the disaccharides as compared with the monosaccharides. The intestinal wall is apparently able to take up to any extent only such sugars as can be utilised by the cells of the organism. For this purpose the disaccharides are useless; cane sugar or

lactose introduced into the blood vessels or subcutaneously is excreted quantitatively in the urine and, as might be expected, does not increase in any way the glycogen of the liver. When maltose is injected in the same manner, a certain proportion of it is utilised owing to the fact that the blood and fluids of the body contain an enzyme, maltase, capable of converting the disaccharide into the monosaccharide, glucose. The absorption of these disaccharides occurs, therefore, much more slowly from the intestine than does the absorption of monosaccharides, the process of absorption being always preceded by the process of hydrolysis. Thus, huge doses of cane sugar may be taken without causing the appearance of cane sugar in the blood or urine. It has been found that sugar does not appear in the urine until as much as 320 grammes of cane sugar have been ingested, whereas any quantity of glucose over 100 grammes may give rise to slight glycosuria. Lactose is absorbed still more slowly. The behaviour of the intestinal wall to the non-assimilable sugars of artificial origin has not yet been sufficiently investigated. It would be interesting to inquire whether the rate of absorption of the different sugars is in any way determined by their stereoisomeric configuration, whether for instance *l*-glucose would be absorbed as rapidly as the ordinary *d*-glucose.

THE ABSORPTION OF PROTEINS

The products of protein digestion are absorbed by the blood vessels. There is no significant increase in the amount of lymph flow or in the amount of protein contained in this lymph during digestion. The small increase observed by Asher and Barbera would be sufficiently accounted for by the increased blood supply to the intestines during digestion. Moreover, it was shown by Schmidt Mülheim that the absorption of proteins was not interfered with as the result of ligature of the thoracic duct and that, after this duct had been ligatured, the ingestion of proteins was followed at the usual interval by the increased output of urea which is the invariable concomitant of protein absorption and assimilation. We must therefore conclude that the products of protein digestion are taken up by the epithelial cells, and passed on by these into the blood vessels.

During the absorption of a protein meal, changes have been described by various observers in the structures of the villus. In nearly every case there is marked increase in the number of mitotic figures in the epithelium lining the follicles of Lieberkühn. According to Hofmeister there is during absorption an increase in the number of leucocytes in the villi, and this observer ascribed an important function to these cells in the absorption of protein. Heidenhain showed that this increase of leucocytes was not constant in all animals, bore no relation to the amount of absorption that was taking place, and was quite inadequate to account for the total absorption that was carried on. On the other hand several observers have described changes in the epithelium as the result of protein digestion. According to Reuter the epithelial cells become swollen, their protoplasm stains less deeply, and at their basal ends the cell limits disappear, the protoplasm being apparently distended with hyaline coagulable material.

The digestive juices finally reduce the proteins to a mixture of amino-acids, with a certain remainder of polypeptides which do not undergo further disintegration under the action of the intestinal enzymes. The final products give no biuret test. The first question we have to decide is to what extent the proteins are reduced to their ultimate hydrolysis products before absorption. We have evidence that serum protein may be absorbed by the small intestine without having undergone any hydrolysis whatsoever. In a series of experiments made by Friedländer, the absorptions of various proteins were

compared after their introduction into loops of the small intestine which had been washed free from enzymes. During a period of three hours this author found that 21 per cent. of the proteins of egg white or of blood serum was absorbed. During the same period, of alkali albumin which had been introduced into the loops, 69 per cent. was absorbed. On the other hand, when syntonin or casein were introduced into the intestine, no absorption whatever was observed. As to the condition in which such unchanged protein reaches the blood stream, our knowledge is still imperfect. Foreign proteins, such as egg albumin, or the serum of other species introduced into the blood stream, may cause poisonous effects and give rise to albuminuria, to lowering of blood pressure, or to alteration of the coagulability of the blood. If injected in small quantities they excite, as a reaction on the part of the organism, the production in the blood serum of a *precipitin*, and the presence of the precipitin may therefore be looked upon as a test by which we may decide whether these proteins have passed through the intestinal wall unchanged. In most cases it is found that, however abundant the amount of protein administered in the soluble form, none of it appears in the urine, nor is any precipitin formation aroused. Ascoli, however, has observed such results occasionally to follow the administration of large doses of egg white, and it has been shown that there is a difference in the behaviour of animals to the introduction of soluble protein into their alimentary canal, according to age. It seems that during the first few days of life the cellular lining of the alimentary canal is permeable to foreign proteins, whereas later on any protein which is absorbed unchanged from the gut does not arrive in the same unchanged condition in the blood stream.

The absorption, however, of unchanged proteins can play but a small part in the assimilation of protein as a whole. Animals very rarely ingest coagulable proteins in a condition in which they will arrive at the small intestine in a state of solution unchanged. In man practically all the proteins of the food are either insoluble or rendered insoluble by the process of cooking. For absorption to take place it is therefore necessary that this insoluble or coagulated protein should be brought into solution, and this process is accomplished by means of the enzymes of the gastric and pancreatic juices.

This process of solution has long been regarded as the chief object of the digestive enzymes. Although both Kühne and Schmidt Mülheim were aware of the production of amino-acids such as leucine and tyrosine as the result of digestion, they regarded their production as evidence of a waste of material. Proteoses and peptones are soluble, diffusible, and rapidly absorbed from the alimentary canal, and there is no doubt that a certain proportion of the products of protein digestion are taken up by the absorbing membrane in this form. For many years physiologists were occupied with the problem as to the fate of these peptones and proteoses after their entrance into the mucous membrane. They do not pass as such into the blood. The injection of small quantities of proteose and peptone into the blood gives rise to the excretion of these substances by the kidneys; injection of larger quantities has pronounced poisonous effects, which were first studied by Schmidt Mülheim and Fano. If samples of blood be taken either from the portal vein or from the general circulation after a heavy protein meal, no trace either of proteose or of peptone is to be found in the blood. Salvioli introduced peptone into a loop of gut which was kept alive by passing defibrinated blood through its vessels. At the end of some hours the loop was found to contain a certain amount of coagulable protein, but no trace of peptone, nor was any trace of the latter substance found in the blood which had been passed through the vessels. These observations were interpreted as pointing to a regeneration in the intestinal wall of coagulable protein from the proteose and peptone taken up from the gut.

It is evident that such a conclusion was not justified by the experiments. Cohnheim found that, although it was perfectly true that proteose and peptone disappeared when intestinal mucous membrane and peptone were placed together in the presence

of either blood or Ringer's fluid, this disappearance was due, not to a regeneration of coagulable protein, but to the fact that the erepsin of the mucous membrane carried the process of hydrolysis a step further, converting the proteoses and peptones into the ultimate crystalline products of protein hydrolysis. Similar observations were made by Kutscher and Seemann, who showed that at any time after a protein meal these end products, especially leucine, tyrosine, lysine and arginine, were to be found in the contents of the small intestine. A repetition of Salvioli's experiment by Cathcart and Leathes deprived this also of much of its significance. It was found that the artificial circulation, although sufficient to maintain the activity of the muscular wall of the intestine, as evidenced by the peristaltic movements, was insufficient to keep the mucous membrane alive. After one hour's experiment the loop contained a mass of epithelial cells mixed with the products of the action of erepsin on the introduced peptone solution. In no case was there any diminution in the amount of uncoagulable nitrogen, *i.e.* there was no formation of coagulable protein, while the processes of absorption had been brought by the desquamation entirely to a standstill.

All the evidence shows that protein, however introduced, whether as coagulated protein or as albumose and peptone, undergoes complete hydrolysis, either in the gut or in the wall of the gut, before entering the blood stream. It should thus be possible to feed an animal on a diet in which the necessary protein had been replaced by the corresponding amount of ultimate products of protein hydrolysis, *i.e.* by a mixture which would give no biuret reaction.

Such a possibility was formerly negated on theoretical grounds by Kühne and by Bunge. It was thought by these observers, either that the animal body lacked the power of synthesis of proteins from these crystalline products, or that any complete hydrolysis occurring in the intestine would involve such a loss of energy to the body as to be unteleological. Neither of these theoretical objections is justified in fact. We know from the researches of Fischer and others that, although the different proteins in our food present a marvellous qualitative similitude, in that all of them yield on hydrolysis the same kinds of amino-acids, there are great differences in the relative amounts and stereo-chemical arrangement of these amino-acids in different proteins. Thus glycine is contained in considerable quantities in gelatin, but is absent from many of the other proteins. Caseinogen is distinguished by the large amount of leucine that it yields, while gliadin, the chief protein of wheat flour, contains very large amounts of glutamic acid. It is difficult to imagine how, for instance, muscle protein could be formed from wheat protein, a process continually occurring in the growing animal, unless we assumed that the protein molecule is first entirely taken to pieces, and that its constituent molecules are then selected by the growing cells of the body and built up in the order and proportions which are characteristic of muscle protein. Moreover, when we measure the amount of energy change involved in the hydrolysis of the proteins, we find it is relatively small. There is not a loss of 5 per cent. of the total energy available —*i.e.* the heat of combustion of the products of pancreatic digestion would differ from that of the original protein submitted to digestion by less than 5 per cent. The energy of the protein as evolved in the body lies, not in the coupling of the amino-acids with one another, nor indeed in the coupling of the nitrogen to the carbon but, like that of the other foodstuffs, in the carbon itself, and is derived from the combustion of the carbon of the molecule into carbon dioxide.

The experimental decision of this question was first attempted by O. Loewi, who found that it was possible to keep a dog in a state of nitrogenous equilibrium on a diet containing fat, starch, and a pancreatic digest of protein which contained no substances giving the biuret test. These results have been confirmed for carnivora by Henderson, by Lüthje, by Abderhalden and Rona, and by Henriques and Hansen. According to Abderhalden, it is possible to keep an animal alive when the nitrogen in his food is represented entirely by the end products of pancreatic digestion. The same result cannot be attained by the administration of the products of acid hydrolysis of protein, but this may be due either to the racemisation of the amino-acids under the action of the strong acid, or to the fact that the

acid splits up certain polypeptide groupings which are still contained in the trypsin digest, and which possibly cannot be synthesised by the cells of the body.

We are justified, therefore, in concluding that while a certain small proportion of the proteins of the food may be absorbed unchanged, a much larger proportion is taken up as proteoses and peptones or as amino-acids. The proteoses and peptones are, however, rapidly changed in the mucous membrane itself into amino-acids, which we may regard as the form in which practically all the protein of the body is presented to the absorbing mechanisms of the alimentary canal for absorption and for passing on into the circulating fluids.

THE FATE OF THE AMINO-ACIDS AFTER ABSORPTION. During a condition of starvation the normal protein requirements of the body, or rather of the active tissues, are met at the expense of the less active tissues. The protein characteristic of any tissue can be taken down, removed to another part of the body, and built up into the protein characteristic of some other active tissue. It is difficult to conceive that such a transference and transformation could occur in any other way than by a more or less thorough disintegration of the protein molecule at one place and its synthesis at the other, and we know from the researches of Hedin and others that every tissue contains intracellular enzymes which are capable of effecting the disintegration of the protein molecule, and are responsible for the autolytic degeneration of tissues after death. If, therefore, the normal interchange of protein between the tissues is accomplished, as we know it to be in plants, by the disintegration of the proteins into their constituent amino-acids and their subsequent reintegration, there is no *a priori* reason to believe that the blood carries the proteins from the alimentary canal to the tissues in any other form than that of amino-acids. The experimental proof of this conclusion was rendered possible by Van Slyke's method for the detection of small quantities of amino-acids in the blood and tissues. In this, after the separation of coagulable proteins by alcohol, the amino-acids are determined by measuring the nitrogen evolved on addition of nitrous acid. Van Slyke has shown that the blood always contains a certain amount of amino-acids, even during fasting. After a protein meal there is a considerable increase in the amount of amino-acids. Thus the blood of fasting animals contains from 3.1 to 5.4 milligrammes amino-acid nitrogen per 100 c.c. Blood taken after food contains from 8.6 to 10.2 milligrammes of amino-acid nitrogen per 100 c.c. The question of the fate of amino-acids thus absorbed from the intestine into the blood is decided by an estimation of the amino-acid content of the different tissues after the injection of amino-acids into the blood. Van Slyke has found that after the injection of amino-acids, only a certain proportion is excreted with the urine, and that the rest of the amino-acids rapidly disappears from the blood and is taken up by the tissues without undergoing any immediate chemical change, though in the case of certain tissues, such as the muscles, a definite saturation point exists which sets the limit to the amount of amino-acids that can be absorbed. On the other hand the capacity of the internal organs, and especially of the liver, for the absorption of amino-acids is much greater.

It is worthy of note, however, that the absorption of amino-acids by the tissues from the blood is never complete, *i.e.* the amino-acids of the blood must be in a state of equilibrium with those of the tissues, although the concentration in the latter may be much greater than in the former. If several hours be allowed to elapse after the injection of amino-acids before the analysis of the tissue is undertaken, it is found that the amino-acid nitrogen

content of the liver may have returned to normal, although the concentration in the muscles has suffered no appreciable fall. Since we have evidence that the circulation of amino-acids through the liver gives rise in this organ to the formation of urea, we must conclude that this organ is especially responsible for the breakdown of the products of protein digestion, which are not directly required for replacing tissue waste. This breakdown must involve a process of deamination. We therefore conclude that the amino-acids normally produced by protein digestion are absorbed without further change into the blood stream. They then circulate throughout the body, as a result of which an equilibrium concentration is established for each amino-acid between the blood and the several tissues, a certain proportion of them finally being built up in each tissue into the proteins characteristic of that tissue in order to replace the waste caused by wear and tear. The rest, probably the major part of the amino-acids, is taken up by the liver, where it undergoes deamination, the nitrogen moiety being rapidly converted into urea and excreted by the kidneys, while the non-nitrogenous moiety is carried to the working tissues to which it serves as a ready and immediate source of energy.

The fact that not only the blood but also the tissues contain amino-acids, even after complete starvation for some days, shows that these substances are intermediate steps not only in the synthesis but in the breaking down of body proteins. Free amino-acids are thus the protein currency of the body, just as glucose is the carbohydrate currency. In the fasting body we must regard the processes of autolysis as the main source of the amino-acids found in the tissues, and it is by autolysis that the proteins of the resting tissues are made available in starvation for those whose continued working is essential for the maintenance of life. The fact that high protein feeding does not appreciably increase the amino-acid content of the tissues shows that any storage of nitrogen in the organism must take place, not in the form of amino-acids, but as body protein.

It was formerly thought that the deamination of amino-acids occurred on a large scale in the wall of the alimentary canal, on the ground that a larger amount of ammonia was present in the portal blood than in the arterial blood. It seems probable, however, that the source of this excess of ammonia is to be found in intestinal bacterial changes, and that the major portion of the amino-acids is actually absorbed unchanged.

THE ACTUAL COURSE OF DIGESTION

London has described the course of digestion of meals of various characters in dogs which had been provided with fistulae in one of the following places: (*a*) gastric fistula (into the body of the stomach); (*b*) pyloric fistula (on the duodenal side of the pylorus); (*c*) duodenal fistula (about 1 foot below the pylorus); (*d*) jejunal fistula (about the middle of the small intestine); (*e*) ileal fistula (just above the caecum).

We may take as an example the course of digestion of a meal composed of 200 grammes of bread. This is eaten by the animal, mixed with the saliva and swallowed. On arriving in the stomach it gives rise to the secretion of gastric juice. On the average 200 grammes of bread evoked the secretion of 20 grammes of saliva, about 10 grammes of mucus from the coats of the stomach, and about 315 grammes of gastric juice. The secretion of gastric juice is continuous during the whole time that the food remains in the stomach. In the animal with a pyloric fistula, one to two minutes after the meal had been taken, a few drops of alkaline fluid were extruded from the opening. From three to eight minutes after the conclusion of the meal, small quantities of clear acid gastric juice were repeatedly extruded. The first admixture of the food with the outflow from the fistula occurred at eight to twelve minutes after the completion of the meal, and after this time the pylorus continued to open at regular intervals of ten to forty seconds, discharging each time a small amount of fluid composed of particles of undigested bread mixed with gastric juice. One and a half hours later the

pylorus began to open less regularly and the fluid became of a more pasty consistence, devoid of lumps of undigested bread. In the fourth, fifth and sixth hours after the meal, the pylorus opened only once every one or two minutes, and towards the end of this period the fluid extruded was clear. The following Table shows the percentage amount of food taken which had left the stomach at the end of each hour after the meal :

First hour		32.6	per cent.
Second hour		17.9	"
Third hour		29.5	"
Fourth hour		1.87	"
Fifth hour		6.66	"
Sixth hour		4.21	"

The large proportion of the ingested food leaving the stomach during the first two or three hours can hardly be regarded as normal. Since in these experiments there was a free outflow from the pylorus and the food was not allowed to enter the duodenum, the local reflex, evoked by the presence of acid in the duodenum, was absent. The gastric contents obtained in this way were analysed in order to find what changes had been wrought on the food by the gastric juice. It was found that 32 per cent. of the bread had been brought into solution. This solution had affected the proteins more than the carbohydrates. Thus 67 per cent. of the nitrogen had been brought into soluble form, consisting chiefly of proteoses and peptones. No amino-acids were formed. Only 25 per cent. of the starch of the bread had been rendered soluble, and of this, 21 per cent. was in the form of dextrin and 4 per cent. in the form of sugar. No absorption, however, either of the digested proteins or of the digested carbohydrates was ever found to take place in the stomach.

The influence exerted by the pancreatic juice, bile and succus entericus poured out on the food in the duodenum, was studied by analysis of the intestinal contents leaving the intestine by a fistula, either at the lower end of the duodenum or in the jejunum or in the ileum. From the duodenal fistula the expulsion of food occurs at repeated intervals but in a somewhat irregular fashion, its movements being determined partly by the contractions of the stomach and partly by those of the duodenal wall. Usually a large gush is followed by a series of small gushes. Although only a foot intervenes between the duodenal fistula and the pyloric fistula, a great difference is observed in the character of the intestinal contents obtained in the two cases. The outflow from the duodenum, being mixed with the pancreatic juice and the bile, is yellow in colour and increased in amount. With a meal of 200 grammes there are secreted on the average 130 grammes of bile and 140 grammes of pancreatic juice. During its passage through the duodenum the carbohydrates of the food undergo considerable changes, so that even one foot below the pylorus we find that one-half to three-fifths of the carbohydrates have been converted into dextrin and sugar. A further digestion of the proteins also takes place amounting to about one-tenth of the whole protein taken with the food.

On deducting the amount of juices which have been added to the food, it is found that even in this short length of intestine absorption has taken place of about one-sixth of the ingested food, about one-fourth of the carbohydrates having been absorbed and about one-eighth of the proteins.

In a dog with a fistula about the middle of its small intestine, the outflow began six to fifteen minutes after the meal, and lasted six or seven hours. The outflow was by small gushes repeated at intervals of five to ten seconds, separated by intervals of one to five minutes during which nothing appeared at the orifice of the cannula. The material obtained was quite different in character from that flowing from the duodenal fistula. The pasty character had disappeared, the material forming a frothy, orange-yellow, even jelly-like mass with practically no trace of undigested bread.

From a fistula in the ileum the outflow occurred at long intervals of three to fifteen minutes and was much scantier than that obtained from the jejunal fistula, consisting of a thick jelly-like, orange-coloured mass. Both proteins and carbohydrates were entirely digested, and in the case of the former the chief products of digestion consisted of amino-acids. Thus in one experiment, after four large meals of 500 grammes of meat each had been given in order to obtain sufficient quantity for analysis, 175 grammes of soluble substances were obtained. From this were isolated tyrosine, leucine, alanine, aspartic acid, lysine, and traces of arginine and histidine.

From a fistula in the cæcum there was no outflow until four or five hours after the meal had been taken. The material from the gut was then extruded in faecal-like masses at long intervals of one half to one hour. This regular outflow lasted for about six hours. The reaction of the contents was strongly alkaline, with no food particles, and the material contained merely débris of cells, with small traces of sugar, dextrin

and unaltered starch. The absorption of the foodstuffs is thus practically complete by the time that the food has reached the lower end of the small intestine.

The following Table gives the total amounts obtained in a series of experiments from the different fistulæ after administration of 200 grammes of bread, and also the percentage amount of foodstuffs which had been absorbed before the food had arrived at the level of the fistula in question :

	Total amounts obtained from 200 grms. of bread.	Absorbed, per cent.
Pyloric fistula . . .	691 grammes	0
Duodenal fistula . . .	691 "	17.45
Jejunal fistula . . .	585 "	37.77
Ileal fistula . . .	412 "	67.65
Cæcal fistula . . .	80 "	94.34

CHAPTER XXX

THE HISTORY OF THE FOODSTUFFS

1.—PROTEIN METABOLISM

IN dealing with the metabolism of the body as a whole, it was pointed out that the proteins taken in with the food might be regarded as having a twofold destiny. One part, and under normal circumstances the greater part, is applied to the production of energy, in this respect discharging a function which might equally well be performed by the fats and carbohydrates of the food. In its second function protein cannot be replaced by any other foodstuff, since it alone contains the necessary elements as well as the groupings of these elements which are essential for the building up of the living tissues. We saw reason to believe that this tissue metabolism accounted, however, for a small part only of the nitrogen of the food. On this account it is possible to ensure health, and a condition of nitrogenous equilibrium, with amounts of protein in the diet of man which may vary between 40 and 200 grammes per diem. The more protein that is taken in with the food the greater is the relative amount which is applied to the energy needs of the body. If, therefore, we would attempt to find out what are the end products of the tissue metabolism, we should confine the energy metabolism of proteins within the smallest possible limits by reducing the quota of protein in the diet to its minimum. Folin has shown that, if we compare the composition of the urine obtained under these two conditions, namely on a diet

DISTRIBUTION OF NITROGEN IN URINE ON VARIOUS DIETS

	July 13 Ordinary diet	July 20 Low protein diet
Vol. of urine	1170 c.c.	385 c.c.
Total nitrogen	16.8 grm.	3.60 grm.
Urea	14.70 grm. = 87.5 %	2.20 grm. = 61.7 %
Ammonia	0.49 grm. = 3.0 %	0.42 grm. = 11.3 %
Uric acid	0.18 grm. = 1.1 %	0.09 grm. = 2.5 %
Creatinine	0.58 grm. = 3.6 %	0.60 grm. = 17.2 %
Undetermined	0.85 grm. = 4.9 %	0.27 grm. = 7.3 %
Total SO ₃	3.64 grm.	0.76 grm.
Inorganic SO ₃	3.27 grm. = 90.0 %	0.46 grm. = 60.5 %
Ethereal SO ₃	0.19 grm. = 5.2 %	0.10 grm. = 13.2 %
Neutral S	0.18 grm. = 4.8 %	0.20 grm. = 26.3 %

containing a normal quantity of protein and on a diet containing a minimal amount, we find evidence of a qualitative difference between the two kinds of metabolism. The difference is well brought out in the Table given here. On a large diet the greater part of the nitrogen can be regarded as derived directly from the food, whereas on a small diet a relatively larger proportion of it must come from protein which has been previously built up

into the tissues. Folin distinguishes these two sources of the nitrogen of the urine as *exogenous*, *i.e.* that from the food, and *endogenous*, *i.e.* derived from the tissues. Two facts stand out in comparing these two urinary analyses. In the first place, on a normal protein diet the urea accounts for 87 per cent. of the total nitrogen of the urine. On an excessive protein diet this percentage may rise to 90 or 95. On a low protein diet the percentage of nitrogen appearing as urea is reduced to 60. On the other hand, practically identical amounts of creatinine are obtained under the two conditions, so that whereas on the full diet it amounts only to 3.6 per cent., on the low protein diet it forms as much as 17 per cent. of the total nitrogen output. We are therefore justified in regarding urea as to a large extent exogenous in origin, and as derived directly from the nitrogenous moieties of protein

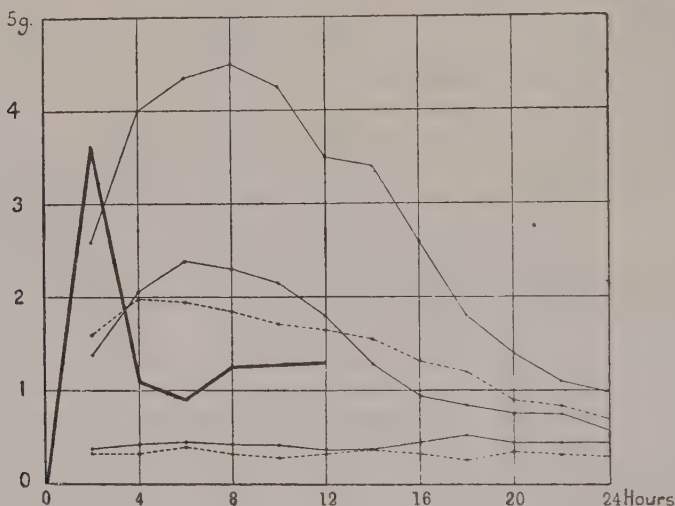


FIG. 323. The Hourly Variation in the Excretion of Nitrogen after a Meal.

The meal was given at 0. The thick line represents the average absorption of the food from the alimentary canal. The thin-lined curves, in order from above, represent the N excretion (1) after a meal of 1000 grammes meat; (2) after 500 grammes meat and 150 grammes fat; (3) after a meal of 500 grammes meat; (4) and (5) both represent the excretion in a fasting animal. (From TIGERSTEDT after FEDER.)

molecules, which may not at any time have formed part of the living tissues of the body.

On giving a large protein meal to a dog, the urea in the urine rapidly rises, and at the end of four or five hours 50 per cent. of the total nitrogen ingested with the food has appeared in the urine as urea (Fig. 323). If we take into account that the digestion of a meat meal in this animal may go on for eight hours, we are justified in the statement that by far the greater portion of the protein nitrogen taken with the food is excreted almost directly after absorption as urea in the urine. Urea is therefore to be regarded in the first place as an index to the amount of protein absorbed. We have seen that the end products of protein digestion in the intestine are the amino-acids. That these are the immediate precursors of the urea is shown by the fact that the administration of these bodies is followed very rapidly by the appearance of the whole of their nitrogen in the urine as urea.

The formation of urea from the amino-acids is accomplished in a very

simple fashion. If amino-acids be treated with the pulp of various organs, there is a production of ammonia, which is not observed when no amino-acids are added to the pulp. Of these, leucine, glycine, tyrosine and cystine give rise to ammonia, while none of this substance is produced from phenylalanine. The production of ammonia is due to the presence of deaminising enzymes in the cells of various tissues. According to van Slyke the liver plays the chief part in the breakdown of amino-acids, though there is no reason to deny the possession of similar powers to other tissues, *e.g.* the muscles. As a result of this deamination ammonia, or some other simple nitrogen compound such as cyanic acid, is set free in the body, and this is rapidly converted into urea. Whether it is cyanic acid, or ammonia, or ammonium cyanate which ultimately enters the circulation is uncertain, but in either form it will be quickly changed into urea, for cyanic acid would rapidly yield a mixture of ammonium carbonate, carbamate, and cyanate. The ammonium

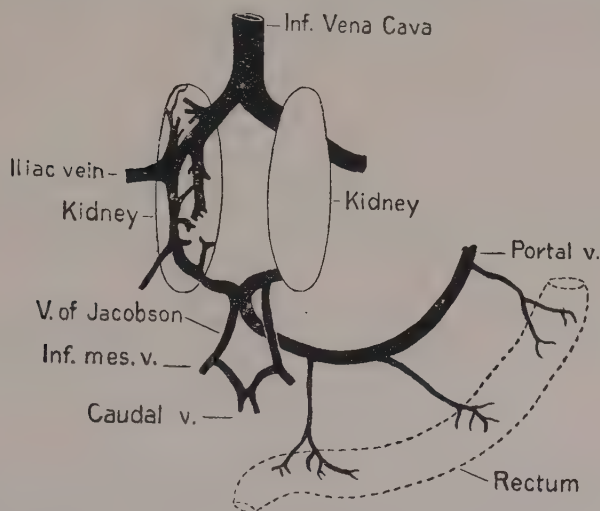
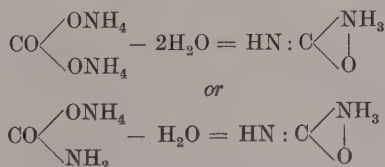
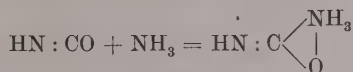


FIG. 324. Diagram to show the Arrangement of the Veins in the Bird, with the Communication of the Renal and Portal Veins. (After MORAT.)

carbonate loses 2 molecules of water and the ammonium carbamate 1 molecule, as follows :



while from ammonium cyanate urea is formed by a molecular rearrangement.



Although there is normally a small amount of ammonia in the urine, it is not increased by injection or administration of ammonium carbonate or carbamate. Either of these two substances administered to man or to an animal gives rise simply to a corresponding increase in the urea of the urine. A large body of evidence points to the liver as being the chief seat of con-

version of ammonia salts into urea. Thus Schröder showed that the liver, even after removal from the body, has the power to transform ammonium carbonate into urea. Defibrinated blood mixed with ammonium carbonate was passed for one hour through a surviving liver. It was then found that the ammonium carbonate had disappeared and that its place was taken by urea, which could be extracted in a crystallised form.

Confirmatory evidence of this removal of ammonia by the liver was supplied by Schröder's experiments on birds. In these animals the chief nitrogenous excretion is not urea, but ammonium urate. In birds there is a communication between the portal system and the general venous system by means of the vein of Jacobson, which connects the lower branches of the portal vein with, as a rule, the left renal vein (Fig. 324). On this account the liver can be cut out of the circulation without entailing the rapid death of the bird, which may live, and pass urine, for three or four days after the operation. The urine is, however, fluid, and the uric acid, instead of accounting for 60 per cent. of the total nitrogen, now forms only 5 per cent. The place of the greater part of the uric acid has been taken by ammonium lactate, which therefore seems to be the chief immediate precursor of the uric acid in the urine of birds. We shall have occasion to consider the method of transformation of ammonium lactate to uric acid more fully when dealing with the origin of the latter.

It is impossible to perform similar experiments in mammals, since ligature of the portal vein, which would be a necessary step in the extirpation of the liver, causes the blood to be dammed up behind the ligature in the portal area. The intestinal wall gets full of effused blood, and the animal dies within a few hours, being bled to death, so to speak, into its portal vessels. A way of partially obviating this difficulty was suggested by Eck, and was carried out by Pavlov. Before ligature of the portal vein, this vessel was joined to the vena cava, so that after the ligature the portal blood could flow directly into the inferior vena cava without passing through the liver (Eck fistula). The liver was not removed, and some animals operated on in this way showed no abnormal symptoms whatsoever, because there was a rapid formation of a collateral circulation so that the blood could get round to the liver. Under all circumstances a path to the liver was still open by the hepatic artery, but to arrive here the blood from the alimentary canal had first to pass through the general circulation. A certain number of animals were susceptible to the nature of their diet. On a diet largely consisting of carbohydrates they maintained good health. After a large meat meal, however, they became ill, and died with convulsions ending in coma.

Pavlov and Nencki ascribed these symptoms to an accumulation of ammonia in the blood, and considered that had the liver been functioning this would have been converted into urea. Their experiments were inconclusive however, because the liver was still present and provided with a large, though abnormal, circulation.

More satisfactory experiments were performed by Mann and Magath and their collaborators, by complete removal of the livers of dogs. The operation is performed in three stages. First an operation like an Eck fistula is performed, except that the vena cava and not the portal vein is tied above the anastomosis. After recovery from this, it is found that collateral circulation is soon established between the portal vein and thoracic veins, *e.g.* the internal mammary and azygos. When this has occurred, the second operation, *viz.* ligature of the portal vein at the portal fissure, is performed. Now all the portal blood flows by the collaterals to reach the inferior vena cava above the liver. Lastly, the hepatic artery is ligatured and the liver removed, together with the length of inferior cava into which its vessels drained.

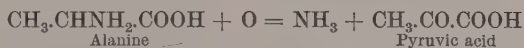
These experiments have shown that after total extirpation of the liver in dogs, both the formation of urea and the deamination of the amino-acids cease completely, indicating that under normal conditions both these processes are carried out in the liver.

The animals only survive the last operation for a few hours, but during that time the urea content of the blood and urine steadily falls. If the kidneys are also removed, the urea of the blood remains constant. When amino-acids are injected into the blood after hepatectomy, the greater part

is recoverable from the blood and tissues, and there is no rise in urea or ammonia. In the normal animal, amino-acids are rapidly changed to urea.

We thus see that the urea, which appears in the urine so rapidly after the ingestion of protein, does not signify a total disintegration of the protein molecule, but is merely the result of the throwing off of the nitrogenous part of the protein molecule by a process of deamination.

The investigation of the stages in deamination, and indeed in the disintegration of aliphatic derivatives generally, is rendered difficult by the fact that all the intermediate products undergo further change and leave the body in a state of complete oxidation as carbon dioxide and water. If, however, an amino-acid group be administered as part of an aromatic compound, *e.g.* forming a side chain of the benzene ring, it is protected from complete oxidation by the stability of this ring. The oxidation of the fatty side chain may proceed to a certain degree, so that intermediate products of metabolism may be excreted still attached to the benzene nucleus. In the α -amino-acids the point where disintegration first occurs is the α -group. Deamination Knoop finds most usually associated with oxidation. The primary product is therefore an α -keto-acid. Thus from alanine the body would produce pyruvic acid :



On the other hand, these keto-acids may undergo reduction to a hydroxy-acid, or be oxidised to a lower fatty acid, though the conditions which determine whether oxidation or reduction shall take place have not yet been fully studied.

Dakin and Dudley have shown that under appropriate conditions (removal of the aldehyde as an insoluble compound) alanine may break up in watery solution into pyruvic aldehyde and ammonia, thus :



and this may be a preliminary to the formation of pyruvic acid.

This loss of nitrogen diminishes little, if at all, the energy value of the amino-acids of the body. The following Table shows the heat equivalents per gram molecule of some of the amino-acids and their corresponding fatty- and hydroxy-acids :

Substance	Calories per grm. molecule
Leucine	855 }
Isobutylacetic acid	837 }
Alanine	389 }
Propionic acid	367 }
Lactic acid	329 }
Pyruvic acid	279 }

These heat equivalents represent the heat evolved on the total oxidation of the substances in question. In the case of the amino-acids, part of the molecule is not oxidised, the nitrogen leaving the body not as free nitrogen but as urea. To obtain the total possible heat value of an amino-acid to the body, we must subtract from its molar heat equivalent half the heat equivalent of urea, since one molecule of urea is produced from 2 molecules of an amino-acid. The heat equivalent of urea being 80, the physiological heat equivalent of alanine will be 349, as against 329 for lactic acid. Thus even in the case of the smallest molecule, the loss of energy attendant on simple deamination and conversion into the corresponding oxy-acid amounts to little more than 5 per cent., and the proportion will be much smaller in the case of the larger

molecules. We are accustomed to regard the urea excretion as an index to protein metabolism. In truth it is an index only of the deamination of the protein constituents, and it tells us nothing whatever about the fate of that non-nitrogenous part, which contains 95 per cent. or more of the total energy of the protein food. The rapid excretion of urea after a protein meal was regarded both by Voit and by Pflüger as a sign that the cells of the body preferred to use protein if it were available. We see now that it affords no basis for this view, but is rather a sign that the body, after satisfying its modest needs for the repair of its tissue waste, has no need for the rest of the nitrogen, and that this is got rid of before the really valuable energy-giving part of the protein molecule is admitted into the metabolic cycle of the cells.

The important problem in the *energy* metabolism of protein is thus the fate and nature of the substances that are left after deamination. We have seen that the protein, when taken as a food, more than either of the other two kinds of foodstuffs, causes a direct augmentation of the respiratory exchanges of the body. Lusk has shown that this specific dynamic action of protein is possessed also by certain of the amino-acids resulting from its decomposition, but not by all. Thus while glycine and alanine exert a well marked specific dynamic action, glutamic acid, leucine and tyrosine have little or no effect upon heat production. The question then arises whether this increased heat production resulting from the ingestion of glycine is due to the rapid disintegration and oxidation of the glycine molecule itself, or is due to a direct stimulating action upon the body cells. The question was decided by giving glycine to an animal which had been rendered diabetic by the injection of phloridzin. Under these circumstances glycine is converted quantitatively into glucose, which is excreted in the urine, so that the CHO moiety of the glycine molecule undergoes no oxidation in the body. Notwithstanding this fact, glycine produces the same augmentation of metabolism in the phloridzinised animal as it would in a normal animal. The same results were obtained with alanine; so it must be concluded that the specific dynamic action of protein is due to the quality possessed by certain of the amino-acids of stimulating the cells of the body and raising their rate of metabolism. But it is not the amino-acids themselves that are the stimulants. This is shown by the fact that, when amino-acids are built up to form new tissues, as in the baby or in the animal recovering from starvation, they exert no specific dynamic action. This action occurs only *when the amino-acids undergo deamination*, and must therefore be the result of the *products of this deamination*. We know, in fact, very little concerning the nature of the substances that are left after deamination, though we have definite evidence that part of this non-nitrogenous moiety of the protein molecule may be converted into sugar or glycogen. Thus, of the amino-acids formed by the digestion of proteins, glycine, alanine, aspartic acid and glutamic acid can be converted quantitatively under appropriate circumstances into glucose. On the other hand, leucine, phenyl alanine and tyrosine yield no glucose, even in the diabetic animal; but may in the liver undergo conversion into aceto-acetic acid, which is a stage in the oxidative disintegration of fats. We need, however, considerably more evidence as to the extent to which deamination occurs and as to its conditions and end products before we can hope to determine the cause for the rapid breakdown of these end products in the body.

The Fate of Arginine

There is one other method by which urea may be formed. Nearly all the ordinary proteins contain arginine, which can be regarded as formed by a

coupling of guanidine with amino-valerianic acid and as analogous to creatine, which is methyl guanidine acetic acid. On heating either of these substances with baryta water, it undergoes hydrolysis and is decomposed with the formation of urea and, in the case of arginine, α - δ -diamino-valerianic acid; in the case of creatine, methyl amino-acetic acid or sarcosine. It has been shown by Dakin and Kossel that the same change may be effected under the agency of an enzyme, arginase, which is contained in extracts of the intestinal wall or of the liver. Possibly a certain small proportion of the urea, which appears in the urine after the ingestion of protein, is due to this hydrolytic splitting of arginine. The other moiety of the arginine, namely the diamino-valerianic acid, probably undergoes the same changes as the other amino-acids.

THE SYNTHESIS OF AMINO-ACIDS. Many, though not all, of the processes in the body are reversible. If the body can effect deamination of an amino-acid, there seems no reason why it should not carry out the reverse change and synthesise an amino-acid from its corresponding ketonic acid and ammonia. Knoop found that the next higher homologue of phenyl alanine, namely phenyl- α -amino-butyric acid, when administered to an animal, was excreted in large quantities in the urine as an acetyl derivative, which was easily isolated in a state of purity. If, then, this amino-acid were formed in the body, one might expect to find it without difficulty in the urine. Knoop found that the administration of phenyl- α -keto-butyric acid led to the excretion of the corresponding amino-acid in the urine. Since keto-acids occur as the ordinary products of the breakdown of amino-acids, it is evident that the animal body can add ammonia and form amino-acids from them.

If the phenyl derivative of the corresponding hydroxy-acid, α -hydroxy-butyric acid, was administered, this was also excreted as the amino-compound. This and other evidence suggests that amino-, keto- and hydroxy-acids are interconvertible in the body, the connecting link being the keto-acid, *e.g.*



These changes can be effected by the perfused liver as readily as by the whole body.

The keto- or hydroxy-acids need not be derived from proteins at all but, like lactic acid, result from carbohydrate metabolism. Thus, if the fitting non-nitrogenous food be given (*e.g.* hydroxy-acids, or carbohydrates from which these bodies may be formed), part of the nitrogen set free by protein disintegration might be recombined with the formation of amino-fatty acids, without giving rise to urea or appearing in any way in the nitrogen balance-sheet of the body. This possibility enjoins the necessity of caution in interpreting the results of metabolism experiments, where the nitrogen excreted is taken to represent the total protein metabolism of the body.

Are the Amino-acids interconvertible?

Although the animal organism is apparently capable of synthesising amino-acids from ammonia and the corresponding keto- or hydroxy acid, it is unable to convert one amino-acid into any other. On this account many proteins are inadequate as food substances since they do not contain the necessary amino-acid groups. Life cannot be supported on such bodies as zein or gelatin, which are lacking in the tryptophane and tyrosine groups. The failure in these cases is owing to the fact that in the animal the means is wanting for the manufacture of some of the radicals which form the non-

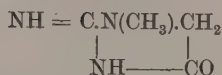
nitrogenous part of the amino-acids. This view receives confirmation from the fact that the glycine and alanine can be easily manufactured in the body.

THE EXCRETION OF AMMONIA. A large proportion of the urea appearing in the urine after a protein meal is exogenous and is derived from the proteins or their disintegration products almost immediately after their absorption. A certain small proportion of the nitrogen in the urine is generally turned out in the form of ammonia. This proportion is not increased by the administration of ammonium carbonate. If ammonium chloride be given to a starving rabbit, it appears in the urine unchanged, and so increases the proportion of ammonia in this fluid. If, however, the ammonium chloride be administered with sodium bicarbonate or with the ordinary vegetable diet, there is no increase of the ammonia in the urine, the whole of the ammonium chloride being converted into urea. The factor which determines the proportion of ammonia in the urine is the relative proportion of acids and bases which have to be eliminated from the body. The normal acid reaction of urine is due to the presence of such substances as acid sodium phosphate. If the fixed alkalis in the food are sufficient to combine with the whole of the acids excreted from the body, then the urine is neutral and the ammonia will be completely converted into urea and eliminated as such. If, however, a dose of mineral acid be administered to an animal, this must be excreted in combination with some of the base from phosphates; the urine will then be acid, owing to a preponderance of monobasic phosphate. Some of the acid will also be excreted in combination with ammonia. The ammonia of the urine is therefore an index to the amount of acids which are excreted. These acids may be introduced directly with the food, as when mineral acids are administered by the mouth, or may be the product of abnormal metabolic processes occurring in the body. Thus under certain circumstances, *e.g.* in complete carbohydrate starvation, hydroxy-butyric acid and aceto-acetic acid are produced in the body in large quantities, but cannot undergo further disintegration. The maintenance of a normal concentration of hydrogen ions (neutrality) in the fluid media of the body is a necessary condition for the continuance of life. It is therefore essential that the acids thus formed should be neutralised, carried to the kidneys, and excreted by them in combination with some base. When the alkalis of the food and of the tissues do not suffice for their neutralisation, ammonia, which is a constant intermediate stage in the production of urea, is then utilised for this purpose and the acids appear in the urine in combination with ammonia. The ammonia of the urine therefore gives valuable information as to the formation of acids in abnormal quantities during the processes of metabolism.

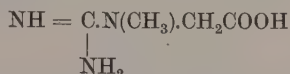
THE ENDOGENOUS OR TISSUE METABOLISM OF PROTEINS

CREATININE. On comparing the output of the various nitrogenous excreta given in Folin's Table quoted above (p. 615), we see that on a low protein diet, when the exogenous metabolism of this foodstuff is reduced to a minimum, the only substance which does not undergo simultaneous diminution is the creatinine. Whereas on an ordinary diet free from meat it accounts for only about 3 per cent. of the total nitrogen output, on the low diet it forms as much as 17 per cent. The conclusion at once suggests itself that creatinine, more than all the other constituents of the urine, might be regarded as an index of the tissue metabolism of protein. Let us see what facts can be adduced in favour of this view.

Creatinine has the formula :



and may be regarded as derived by a process of dehydration from creatine (methyl guanidine acetic acid).



It may be formed from this latter substance by boiling with strong hydrochloric acid. Creatine has long been known as the most abundant nitrogenous extractive in the body. It exists in relatively large quantities in muscle and it has been calculated that the body of a man at any time contains about 90 grammes of this substance.

Creatinine is certainly to be regarded as a waste product. The question at issue is whether it is to be regarded as an invariable end-product of the metabolism of tissue protein, or whether it represents the terminal phase of a metabolic process quite apart. There is much accumulated evidence that the urinary creatinine is derived from creatine. But the analyses given in Folin's table show that creatinine is excreted in considerable quantities even when the man is on a creatine-free diet. It has been found, moreover, by Folin that creatine administered by the mouth may disappear in the body. It would seem probable that this is due to its conversion into phosphagen which is stored in the muscles, of which it forms an invariable and essential constituent. If a larger amount be given, creatine appears as such in the urine. In most cases a certain minute proportion is excreted in the form of creatinine. Under abnormal circumstances, *e.g.* during illness when the physiological activities of the body are lowered, a portion of the creatine may be found in the urine in an unchanged condition. If creatinine is to be regarded in any way as the index of tissue metabolism, its amount ought to vary with the extent of this metabolism. Thus it should be increased when there is an exaggeration of the disintegrative processes in the tissues, and should be diminished when the nutritive changes in these tissues, especially in the muscles, are reduced to a minimum. The end products of tissue metabolism therefore should be increased under the following conditions:

(1) Increased motor activity involving increased wear and tear of the muscular tissues.

(2) In fevers, especially in those where there is severe toxæmia and rapid wasting of the muscles of the body.

On the other hand it should be diminished where the activity of the muscular tissue is reduced to a minimum, as under the influence of sleep or soporifics, or where the bulk of the muscular tissue is reduced, as well as its activity, as in cases of widespread muscular atrophy and paralysis. The excretion of creatinine has been investigated under these various conditions by van Hoogenhuyze and Verploegh, and their results bear out the view expressed above as to the intimate relation of creatinine with the tissue metabolism. During and immediately after muscular exercise, there is an accelerated output of creatinine in the urine, but there is a corresponding drop during recovery, so that the daily excretion is but little affected. Since we know that during muscular contraction there is a conversion of phosphagen into creatine and an inorganic phosphate, both of which are readily diffusible, it is reasonable to suppose that some of the creatine escapes into the general circulation, is converted into creatinine, and excreted as such. During

recovery it is possible that the process may be reversed, or at all events checked, as creatine phosphate is re-formed.

According to this view, therefore, we must regard creatinine as the direct product, not of protein metabolism, but of the metabolism of the muscle as a whole. That the creatine from which it is formed ultimately arises from protein is extremely probable, though by what intermediary stages it is impossible to say. Any small amount of creatine which escapes from its proper combination is converted into creatinine, while larger amounts are excreted unchanged. The greater the mass of muscle in the body, or the greater its rate of destruction, the greater will be this liberation of creatinine.

During protein starvation the uric acid output, though diminished, does not show a change which is at all proportional to that shown by the urea. This substance therefore might also represent an end product of tissue metabolism. Since, however, uric acid is an outcome of the metabolism of a special group of bodies, the nucleins and purine bases, we shall have to devote a complete section to its consideration.

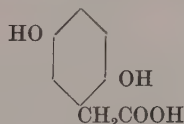
Although the urea is diminished in protein starvation, it still remains the most abundant nitrogenous constituent of the urine. We are therefore not justified in excluding this substance from the products of tissue metabolism. We shall see later that uric acid may possibly also undergo further oxidation with the formation of urea. Even during complete protein starvation, some of the urea which is turned out may be the expression of a utilisation of protein through deamination for the energy needs of the body.

SULPHUR. Sulphur occurs in the urine in three forms: as ordinary inorganic sulphates, as ethereal sulphates (indoxyl- and skatoxyl-sulphates), and in an unoxidised condition often termed neutral sulphur. Part of this last consists of cystine, part of thiocyanates, and in some animals mercaptan compounds. The excretion of the inorganic sulphates rises *pari passu* with that of the urea so that, very soon after the throwing off of the NH_2 group, there must be also a removal and oxidation of the greater part of the sulphur contained in the cystine group of the protein molecule. So far as regards the metabolism of the body as a whole, the ethereal sulphates may be classed with the inorganic sulphates. They are excreted in varying quantity according to the extent of the decomposition processes which are occurring in the intestine. Under the influence of these processes the tryptophane, produced in the pancreatic digestion of proteins, is converted into indol and skatol. These two substances, after absorption, are deprived of their poisonous qualities by oxidation and conjugation with sulphuric acid to form the indoxyl- and skatoxyl-sulphates of the urine, both of which are innocuous. If the processes of putrefaction are increased, as in intestinal obstruction, the relative amount of sulphate appearing in the conjugated form is also increased. On administration of phenol, a large proportion of the sulphate appears in the urine conjugated with phenol or with products of its oxidation. If the normal putrefactive processes which go on in the intestine are abolished by the administration of intestinal antiseptics such as naphthalene or calomel, the ethereal sulphates practically disappear from the urine. We cannot therefore regard the absence or diminution of the ethereal sulphates during protein starvation as throwing any light on the endogenous protein metabolism. On the other hand the fact that the neutral sulphur undergoes no decrease suggests that this part of the sulphur output of the organism may be connected with tissue metabolism. Further observations on the output of neutral sulphur during fever or wasting diseases are necessary before a definite conclusion can be arrived at on this point.

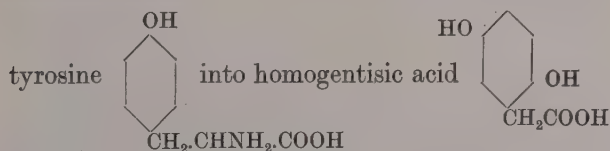
THE FATE OF THE AROMATIC AND OTHER CYCLIC GROUPS IN THE PROTEIN MOLECULE

So far, we are acquainted with three compounds of the aromatic series among the products of disintegration of the protein molecule. These are tyrosine, phenyl alanine and tryptophane. Since these substances are also contained in the protein constituents of the tissues, we may assume that, after they have been set free by the digestive hydrolysis of proteins, they are absorbed and built up again with the other amino-acids in appropriate groupings. Like these they are susceptible of complete oxidation in the body, so that they can contribute to the supply of energy. Any one of these substances, administered with the food or subcutaneously, is entirely destroyed, with the production of urea, carbon dioxide and water. In this respect they present a marked contrast to almost all other compounds of the aromatic series. In these we find that the benzene ring is extremely stable. Thus benzoic acid, benzylalcohol and phenyl propionic acid, when administered, are passed in the urine as hippuric acid (benzoyl glycine). Indol and skatol, which are closely allied to tryptophane, undergo oxidation in the body without further modification and appear in the urine as conjugated aromatic sulphates.

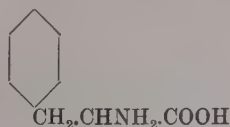
Some light is thrown on the conditions of breakdown of these aromatic bodies by the study of a rare disorder in metabolism, which may occur in certain families and is known as *alcaptonuria*. In this condition, which is congenital and lasts throughout life, the urine darkens considerably when made alkaline and exposed to the air. It has the power of reducing Fehling's solution, so that the presence of sugar might be suspected. On analysis the peculiarities of the urine are found to be due to the presence in it of a substance known as homogentisic acid. This is dihydroxyphenyl acetic acid.



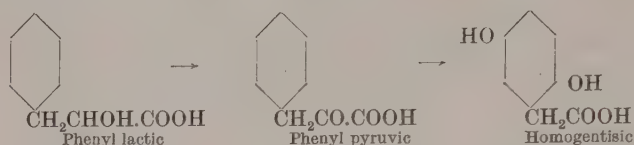
The amount of this substance in the urine bears a constant ratio to the nitrogen excreted. If tyrosine or phenyl alanine be administered to patients affected with this disorder, both substances are quantitatively converted into homogentisic acid. The ratio of this acid to the total nitrogen indicates that the whole of the tyrosine and phenyl alanine of the protein molecule, whether set free in the alimentary canal or in the tissue metabolism, is converted into homogentisic acid. It is not possible to conceive of the direct conversion of



The tyrosine might first be reduced to phenyl alanine



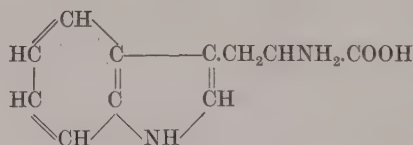
and then this substance might undergo oxidation into homogentisic acid. Since phenyl lactic acid and phenyl pyruvic acid, but not phenyl acetic acid, are also converted in alcaptonuric patients to homogentisic acid, it has been suggested that these two substances form stages in the conversion of phenyl alanine into homogentisic acid. Thus



It is further thought that under normal circumstances the phenyl derivatives, tyrosine and phenyl alanine, are oxidised to homogentisic acid as in the alcaptonuric patient. In the normal individual, however, the introduction of two hydroxyl groups into the benzene ring leads to some process, perhaps of an enzyme character, which breaks up the ring. This enzyme is absent in the alcaptonuric, so that the transformation of the phenyl derivatives stops short at the stage of homogentisic acid (Garrod). The eminently specific character of this process is shown by the fact that, although these various substances undergo complete oxidation in the body, a slight modification in the series of conversions renders further change impossible. Thus if the side group in phenyl lactic or phenyl pyruvic acid be converted to acetic acid before the introduction of the two OH groups into the phenyl ring, the phenyl acetic acid thus produced is incapable of undergoing further oxidation.

Tyrosine in the intestine may undergo deamination to form hydroxyphenyl propionic acid and hydroxyphenyl acetic acid. These cannot be further oxidised, but appear in the urine as such or, after conversion into cresol or phenol, as sulphuric acid esters.

Somewhat similar conditions apply to the oxidation of tryptophane. This body is an indol derivative and consists of a benzene ring and a pyrrol having two of their carbon atoms in common. Its formula is:—



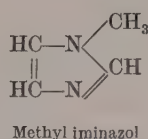
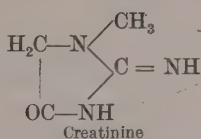
i.e. it is indol amino-propionic acid. It undergoes, like tyrosine, complete oxidation in the body. On the other hand a very slight alteration in the molecule renders it incapable of this change. Thus some of the tryptophane set free by the tryptic digestion of proteins may, under the influence of the putrefactive bacteria of the intestine, undergo deamination and reduction with the production of indol propionic acid, and this by oxidation may be converted to indol acetic acid. The latter substance by decarboxylation may be converted into skatol or, by oxidation and further loss of carbon dioxide, into indol. Of these products of bacterial change, indol acetic acid may be found in the urine, and indol and skatol are oxidised to the corresponding phenols and pass into the urine conjugated either with sulphuric acid to form "urinary indican," or with glycuronic acid.

Apart from these putrefactive changes due to bacteria, no indol derivatives pass into the urine. The amount of the indol and skatol esters serves

therefore as an index of bacterial decomposition in the alimentary canal, but gives no clue to the total tryptophane metabolism of the body. If putrefaction be prevented by the administration of calomel or other intestinal antiseptic, these esters may entirely disappear from the urine. On the other hand, the partial obstruction to the onward passage of food, caused by dividing the small intestine in two places a few inches apart and replacing the intervening length of intestine the wrong way round, increases the indican excretion twenty or thirty-fold. Subcutaneous injection of tryptophane in rabbits does not increase the indoxyl and skatoxyl sulphates ('urinary indican') in the urine, whereas a considerable increase is brought about by subcutaneous injection of indol.

The pyrrol ring, which occurs in proteins as proline and hydroxyproline (*i.e.* pyrrolidine carboxylic acid and hydroxypyrrolidine carboxylic acid) appears to undergo complete disintegration in the body. This ring is of interest since it appears to take an important part in the building up of hæmatin, the essential prosthetic group of hæmoglobin.

Another ring grouping, iminazol, occurs in histidine, which is iminazol α -amino-propionic acid. This, too, undergoes complete oxidation in the body. It is important to bear in mind that this ring may be produced synthetically by very simple means, *e.g.* by the action of zinc oxide and ammonia on glucose, which results in a rich yield of methyl iminazol. The same grouping is found in creatinine, as is seen by comparing the formulæ :



The iminazol group is at present chiefly interesting in that it contributes to the formation of the complex ring compounds known as the purines. Since the purine metabolism is closely connected with the question of the origin of uric acid, we may consider these questions together.

2. NUCLEIN OR PURINE METABOLISM

The nucleoproteins are especially abundant constituents of nuclei, and therefore occur to a greater or less extent in all the ordinary animal foods, eggs and milk excepted. Just as the metabolism of proteins is the metabolism of the amino-acids, so the metabolism of the nucleoproteins and nucleins is essentially comprised in the history of its characteristic constituents, the purines. An account of the chemistry of nucleoproteins has already been given in Chapter IV.

FORMATION OF NUCLEINS IN THE BODY. In the case of the proteins we saw reason to believe that, in the higher animals at any rate, there was little power of converting one amino-acid into another, and that on this account the food had to contain representatives of every amino-acid (or perhaps of the corresponding hydroxy-acid) necessary to the building up of the tissue proteins. The nucleins, on the other hand, can certainly be synthesised by the animal. This is shown by the fact that the hen's egg before incubation contains practically no nuclein or purine bases. During incubation tissues are formed, and there is a rapid increase in the number of nuclei, so that the chick just before it is hatched contains a considerable amount of nuclein from which purine bases can be extracted. This nuclein must have been formed by a synthesis from the phosphoproteins and phosphatides (phosphorised fats) which form so important a constituent of

the egg-yolk ; and in the same way the purines must have been formed by a process of synthesis. There is no definite evidence as to the steps in this synthesis, though there are indications that arginine and histidine may be starting points. The power of synthesis of purines possessed by the body must complicate the question of their fate after ingestion, since it is evident, either that they can be destroyed and excreted in some other form, or that the products of their destruction may be built up into fresh purine or nuclein molecules. In the same way, in the growing child there is a rapid increase in the nuclein of the body, although the only food ingested is milk, which contains but an insignificant amount of nuclein.

FATE OF NUCLEINS IN THE BODY. Nucleins and nucleic acids are dissolved by the pancreatic juice, and the protein part is digested in the usual way. The fate of the nucleic acid of the food is uncertain, though various enzymes have been found in the intestinal juice which convert nucleic acids into mononucleotides ; others capable of converting these into nucleosides and phosphoric acid. Other enzymes (nucleosidases), which break up certain nucleosides into sugars and purine bases, are found in the cells of the intestinal mucosa, so that probably the products absorbed are phosphoric acid, nucleosides, sugar, guanine and adenine.

Ingestion of nucleic acid is, in man, followed by an increased excretion of uric acid in the urine, so that we regard this substance as the end product of nuclein metabolism in the body. It is evident that the uric acid of the urine may be derived either from the nucleins of the food or from the nucleins of the tissues of the body, the uric acid in these two cases being spoken of as exogenous and endogenous respectively. By digestion of nucleic acids with animal tissues or extracts of animal tissues under varying conditions, it is possible to bring about all the changes involved in the conversion of the purine bases contained in them into uric acid. Nucleases are of different kinds, the phosphonuclease splitting off the phosphoric acid and leaving the nucleosides, while the purine nucleases, which are more effective in a slightly alkaline medium, split off the purines, leaving the phosphoric acid combined with the carbohydrate. The purines set free in this way undergo further changes. The hypoxanthine derived from inosinic acid is converted under the action of an oxidase first into xanthine and then into uric acid.

This was one of the earliest facts discovered in the metabolism of purines. Horbaczewski showed that, if spleen pulp be digested with blood for some time, it is possible to extract a considerable amount of xanthine from the mixture. If, however, oxygen be bubbled through the fluid, the xanthine disappears, its place being taken by uric acid.

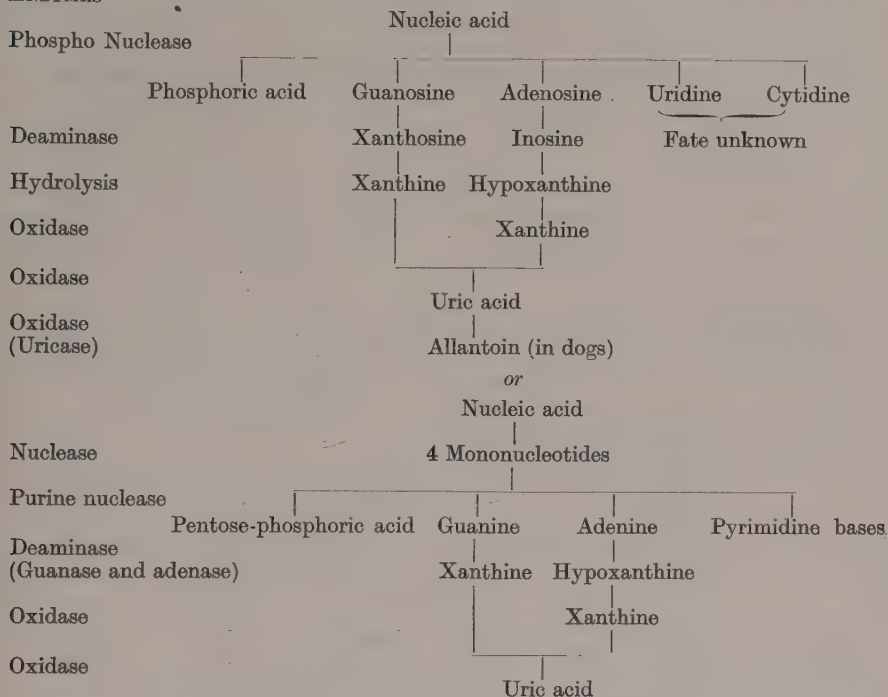
From the more complex nucleic acids the amino-purines, adenine and guanine, are set free. These first undergo deamination under the action of special enzymes, adenase and guanase, and are thus converted into hypoxanthine and xanthine respectively. These bodies subsequently, under the action of oxidases, may be converted into uric acid.

All these changes occur in the living body, though not necessarily in the order just set out. Thus when the pyrimidine derivatives are administered to dogs, they pass out unchanged. If, however, free nucleic acid be administered to the animal, no trace of these derivatives can be found in the urine, so that they must have undergone complete oxidation. In the same way the dog's liver is able to deaminate completely the adenine group of nucleic acid, converting it into hypoxanthine ; but it is without effect on free adenine. It is evident, therefore, that the various enzymes which have been described act partly on the whole nucleotide molecule, partly on the products of its decomposition, and that the results of the action of the body enzymes are not the same in the two cases.

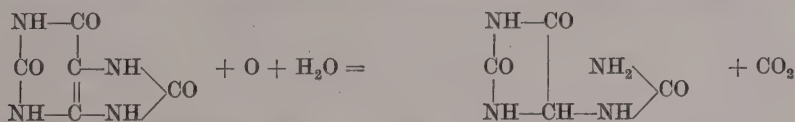
If we make this reservation that the constituent parts of the nucleic acid molecule

may undergo changes while still bound to the other parts, we may represent diagrammatically the formation of uric acid from nucleic acid as follows :

ENZYMES



The question arises whether the uric acid excreted by a man represents the whole of the nucleins which have been destroyed in the body. Although complete equivalence has been found between the amount of hypoxanthine ingested and the amount of uric acid excreted, the same equivalence has not been established in the case of nucleic acid; and the important question arises whether uric acid once formed is stable or whether it may undergo further changes before being excreted. In many animals, such as the dog, the amount of uric acid in the urine is only minute, the chief purine derivative in this fluid being allantoin. Allantoin is formed when uric acid is oxidised with potassium permanganate, the following changes taking place:



The same transformation can be effected by extracts made from the liver of the dog and probably of other animals. The enzyme carrying out this change is known as uricase. No such enzyme is found in human liver or any human organs and, according to Jones and others, uric acid once formed in the human organism is not further oxidised. This is not confirmed by Folin, who considers that a certain varying proportion of the uric acid formed in the human body is destroyed by oxidation, probably in the blood. The small trace of allantoin which may occur in human urine is directly derived from the food.

On the other hand, it is important to bear in mind the possibility that some of the uric acid which occurs in human urine may arise by a process

of synthesis. We have seen already that in the bird the greater part of the uric acid is derived not from purines at all, but by a process of synthesis from lactic acid and ammonia; and though we have no evidence of a similar change occurring in the mammal, we are not able definitely to exclude its possibility.

EXCRETION OF URIC ACID. The complexity of these various processes in man renders it a difficult task to form a clear idea of the origin of the urinary uric acid and of the conditions which determine the variations in the amount excreted at different times. Under ordinary circumstances a man excretes about half a gramme of uric acid per day. In addition the urine contains a small amount of purine bases. From 10,000 litres of human urine Krüger Salomon succeeded in isolating xanthin (10·1 grams), hypoxanthin (8·5 grams), adenine (3·5 grams). These are probably derived from the uric acid metabolism. In addition there are various methylated purines, derived from such constituents of the diet as caffeine, &c.

As we should expect, the amount of uric acid in the urine varies with the diet. The Table below, from Bunge, gives the composition of the urine secreted (1) on a mixed diet, (2) on a diet mainly composed of meat, (3) on a diet mainly composed of bread.

Twenty-four hours.					Mixed.	Meat.	Bread.
Quantity c.c.	.	.	.	.	1500	1672	1920
Urea	.	.	.	gram.	33	67	20
Uric acid	.	.	.	"	0·55	1·3	0·25
Ammonia	.	.	.	"	0·9	2·1	0·9
Creatinine	.	.	.	"	0·77	0·9	0·4
Hippuric acid	.	.	.	"	0·4	—	—
Sulphates	.	.	.	"	2	4·6	1·2
Sodium chloride	.	.	.	"	16·5	7·5	8·2
Phosphates	.	.	.	"	3·16	3·4	1·6
Potassium	.	.	.	"	2·5	3·3	1·3

Calcium, magnesium, iron, colouring matter, gases.

An attempt has been made to arrive at the amount of uric acid produced endogenously, *i.e.* by the breakdown of the tissues, from a study of the quantity of uric acid in the urine under varying conditions of food. During starvation, when the man is living on his own tissues, one might expect the uric acid to be increased in consequence of disintegration of the tissues. It has been suggested that the amount of the endogenous uric acid in the urine would be obtained by an analysis of the urine from patients taking a diet free from purine bases, but containing sufficient nitrogen to maintain nitrogenous equilibrium. It is impossible, however, to arrive at any constant figure for the endogenous uric acid. Even in the entire absence of purine derivatives from the diet, the amount of uric acid increases with the total nitrogenous metabolism. This fact is well shown in the Table by Folin (already quoted) of the composition of the urine on a low and a high protein diet respectively. Although in each case care was taken to exclude purine-containing bodies from the food, the output of uric acid on the high nitrogenous diet was double as much as on the low diet. All we can say is that uric acid is constantly being derived from the tissue

disintegration, but that it varies under different conditions of nutrition as well as under different conditions of activity of the body.

There are two main conditions which give rise to a definite increase in the output of endogenous uric acid. These are (1) severe muscular activity, (2) febrile states accompanied by increased nitrogenous metabolism. Since both these conditions are associated with an increased breakdown of muscle substance, we may regard the uric acid as derived especially from the hypoxanthine or its precursors, such as inosinic acid, contained in the muscle.

The foods which are especially effective in causing increase in the exogenous uric acid are those rich in nuclein, such as sweetbreads or liver, and those rich in hypoxanthine or its precursors, such as meat or meat extract.

When these foods are taken, or when nucleic acid itself is administered, a condition of leucocytosis is generally produced, the number of leucocytes in the blood being increased as much as three times. It has been suggested that the uric acid is

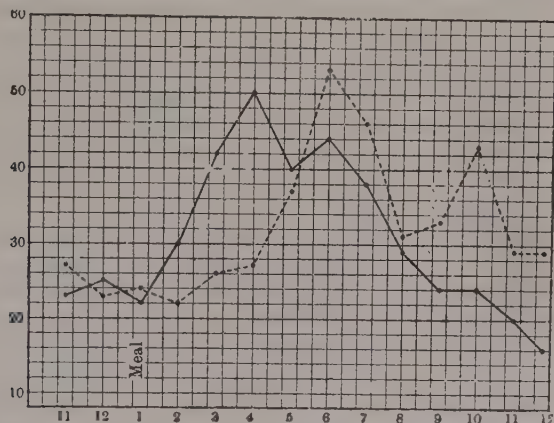


FIG. 325. Curves showing the Hourly Excretion of Uric Acid and Urea after a Single Meal. (HOPKINS.)

The continuous line = uric acid output; the dotted line = urea output.

actually derived from a disintegration of the newly formed leucocytes and not by a direct conversion of the purines of the food. It is quite possible, as suggested by Schittenhelm, that the leucocytes play a part in the transference of the nucleins from the intestine to the circulation. But the absence of any absolute proportionality between the degree of leucocytosis and the amount of uric acid excreted points to the probability of a direct conversion of the purines of the food into uric acid.

URIC ACID IN GOUT. Gout is a condition in which deposits of urate of soda occur in the cartilages of the joints, the great toe joint being the seat of predilection for this disorder. The deposit is generally associated with an acute inflammation of the joint. In normal individuals the amount of uric acid in the blood is about 2 mg. per 100 c.c. Uric acid is readily excreted by the healthy kidneys. If the production of uric acid be much increased by the administration in large quantities of foodstuffs rich in purines, it becomes possible to demonstrate an actual increase of uric acid in the blood. In gout there is constantly an increased amount of uric acid in the blood, probably in the form of sodium urate, even when the patient is on a purine-free diet, so that gout may be regarded, from one point of view at any rate, as an uricæmia of endogenous origin. On the other hand, the output of uric acid in the urine is not increased, and may in fact be somewhat smaller than normal. It might be thought that the presence of uric acid in the blood must therefore be due to diminished power of excretion of this substance by the kidneys. This view is difficult to reconcile with the fact that, if uric acid be injected subcutaneously into gouty subjects, it is stated to be excreted in the urine exactly in the same way, and as rapidly, as in normal persons. It has been

suggested that gout consists essentially in a disturbance in the various enzyme mechanisms which are responsible for the changes undergone by the purines, so that there is an increased amount not only of uric acid itself, but of various intermediate products in its formation from the purine bases of the food and of the tissues. The deposit of the uric acid in the joint cartilages, characteristic of acute gout, appears to be simply a crystallisation of urate of soda from a supersaturated solution of this substance in the blood. Speaking broadly, gout is a disease of the well-to-do. It is almost unknown in the labouring class. It seems, therefore, that it is not so much the supply of purines in the diet which must be controlled as the general conditions of nutrition, which determine the metabolic changes in the purines either of the food or tissues under normal conditions of metabolism.

3. FAT METABOLISM

Fat is found in the body in various situations. In a fat animal the largest amount occurs in the panniculus adiposus in the subcutaneous tissues. Large quantities are also found surrounding the abdominal organs and between the layers of the mesentery and great omentum. In this adipose tissue the fat is enclosed within and distends connective tissue cells, the protoplasm of which is reduced to a thin pellicle round each fat globule. Fat is also found in the form of granules in more highly specialised cells, such as the secreting cells of the liver or the muscle cells. The condition of these cells is often spoken of as fatty infiltration, or fatty degeneration, according to the circumstances which are responsible for bringing about the deposition of fat. We shall have to discuss later on how far we are justified in assuming any real distinction between these two processes. From the physiological standpoint the most important intracellular depôt of fat is in the liver. If this organ be deprived of glycogen and fat by starvation, a fatty meal gives rise to a great deposition of fat in its cells. There is apparently an antagonism between the processes which lead, on the one hand to the deposition of glycogen, and on the other to the deposition of fat. Thus an excessive carbohydrate diet, which induces great deposition of fat in the subcutaneous tissues, causes only the formation of glycogen in the liver. The glycogen must be got rid of before it is possible to cause the deposition of particulate fat. On this account the normal content in fat of the livers of different animals varies with their ordinary diet. Fishes, *e.g.* the cod, which take but little carbohydrate in their food, have generally a very large quantity of fat in their livers. Herbivorous animals, as a rule, have practically no visible fat in the liver.

Fat also occurs in certain secretions, *e.g.* the milk and the sebum, its function in the latter case being mainly protective.

Besides the visible deposit of fat found in adipose tissue and in other situations, a large amount of fat is always present, built up into the protoplasm of the cells in such a condition that its presence cannot be detected by histological means. The presence or absence of visible fatty globules affords very little clue to the total quantity of fat in the cells. Thus in one case the heart muscle, which had undergone extreme fatty degeneration and was loaded with fat globules, contained 19 per cent. of its dried weight of fat. A heart muscle taken from a normal animal at the same time, presenting no visible fat globules, contained 17 per cent. of fat.

COMPOSITION OF FAT. The fats occur generally in the form of triglycerides of various fatty acids. In adipose tissue the acids are chiefly stearic, palmitic and oleic. In certain animals the glycerides of more unsaturated fatty acids occur. Thus lard contains about 10 per cent. of fats belonging to the linoleic series. The fats of cows' milk, though consist-

ing chiefly of the three above-mentioned, include also the esters of lower acids in fair amounts.

The 'fat' extracted from the tissues (*e.g.* heart muscle) includes a considerable amount of 'phospholipides' (lecithins, &c.). This is shown by the fact that there is about one part of ether-soluble phosphorus for twenty to fifty parts of fatty acid. It also contains a much larger proportion of unsaturated fatty acids of the linoleic and even lower series, so that its 'iodine value' is generally found relatively high (120 as compared with 40 to 60 in adipose tissue). Cholesterol is also present to the extent of 5 to 25 per cent. of the amount of fatty acids, though almost absent from adipose tissue. In nerve tissue some of the cholesterol is free, but in most tissues it is combined with fatty acids, instead of glycerol, to form cholesteryl esters. The highest proportion of cholesteryl esters is found in lung, then come kidney, liver, heart and muscle.

FUNCTIONS OF FAT. First must be mentioned the significance of fat as a reserve food store. The power of the organism to store up reserve carbohydrate is strictly limited. The liver of man can probably not accommodate more than 150 grammes of glycogen; and assuming that the muscles of the body may contain an equal amount, 300 grammes represents the extreme limit of storage of carbohydrates in the body. On the other hand, in most animals there is practically no limit to the amount of fat which can be laid down with over-feeding. This fat does not enter into the normal metabolism of the body, but is available for use whenever the needs of the body are increased above its income.

As to the part taken by fat, especially the hidden fat of the 'working cells, in the chemical processes which determine the life of the cell, our knowledge is still very scanty. Fatty acids enter into the constitution of the phospholipides and glycolipides which form important constituents of the protoplasm and limiting membrane of every cell. As constituents of the membrane itself, fatty substances therefore have a protective action, and also regulate the passage of substances into the cell across the membrane.

The presence of the phospholipides as integral constituents of all protoplasm suggests that they may play a part in the normal transformations which occur within the cell, and may represent, so to speak, the currency into which fat is transformed in order to participate in the vital processes, and to be transported and utilised for the needs of the cell.

ORIGIN OF FAT IN THE BODY

The formation of adipose tissue is the result of an excess of income over expenditure. As soon as the latter exceeds the former, the fat store is drawn upon, so that adipose tissue is the one which presents the greatest loss during starvation. As much as 97 per cent. of the adipose tissue may disappear during this process. It is different with the "fat" of the tissues, for here, though there may be loss of fat, there is equivalent loss of protein, which retains its ratio to fat throughout: the cholesterol, however, is not drawn upon to such an extent.

Our first task is to consider what part is played by each in the formation of *dépôt* fat. Can this substance be formed from all three classes of foodstuffs?

FORMATION FROM THE FAT OF THE FOOD. Experiment has shown that the composition of the fat of any animal can be varied within wide limits by alterations in the nature of the fat in the food. This is shown

strikingly in an experiment performed by Lebedeff. Two dogs, after a preliminary period of starvation, were fed, one on a diet containing a large proportion of linseed oil, and the other on a diet containing much mutton suet. After some weeks they were killed, and it was found that whereas the fat of the dog which had been fed on mutton suet was solid at $50^{\circ}\text{C}.$, that of the dog fed on oil was still fluid at $0^{\circ}\text{C}.$ Moreover, by feeding animals with fatty acids not usually found in the body, these are laid down in the adipose tissue. Thus colza oil contains a glyceride of erucic acid, and as Munk has shown, an animal fed on colza oil lays on fat in which erucic acid is present. The same physiologist observed that, after the administration of various fatty acids to a man with a chylous fistula, the glycerides of the corresponding fatty acids made their appearance in the chyle, whether these fatty acids were those normal to man or not. We must conclude, therefore, that the fats taken with the food, if not immediately required for the energy needs of the body, may be laid down without change in the adipose tissues. The mechanisms involved in the translation of fat from the alimentary canal to the tissues probably involve only changes of hydrolysis and re-esterification. The fats are hydrolysed in the gut and are resynthesised to a certain extent in their passage into the epithelium. In the chyle and blood they probably wander chiefly as neutral fats, or, according to Bloor, as lecithins, to be rehydrolysed for their passage into the cells of the body, which they may enter either in the form of soaps or possibly as fatty acids dissolved in some of the constituents of protoplasm.

FORMATION OF FAT FROM CARBOHYDRATES. It has long been the experience of farmers that animals might be fattened on a diet in which carbohydrates predominate.

Definite evidence has long ago been given, especially by Lawes and Gilbert, for the transformation of carbohydrates into fats. In these experiments two young pigs, ten weeks old, of the same litter, with approximately equal weights, were taken. One was killed and the fat and total nitrogen in the body estimated. From the amount of nitrogen the maximum possible quantity of proteins present was calculated. The second was fed on barley for four months. The barley was measured and analysed, as well as the amount of undigested fat and protein that passed through the animal. At the end of the four months the second animal was killed and analysed. It was found that the animal contained 1.56 kilos. more protein and 8.6 kilos. more fat. It had taken up with the food 7.49 kilos. more protein and 0.66 kilo. fat. If we subtract the protein added to the body (1.56) from that taken up with the food (7.49), there is a remainder of 5.93 kilos. which might possibly have given rise to fat. But 7.9 kilos. of fat had been added in the body—a far larger amount than could possibly have arisen from the available protein. At least 5 kilos. of fat in this experiment must have been derived from the direct conversion of the carbohydrates of the food. How and where this conversion takes place is at present quite unknown. The fats formed on a carbohydrate diet are deposited chiefly in the subcutaneous tissue. For the reasons already given the liver is found free from fat under these conditions. In the fat formed from carbohydrate the two high melting point saturated acids, palmitic and stearic acid, predominate. The fats of low melting point, such as olein, are absorbed more readily from the intestine than those of high melting point. Where the fat of the body is chiefly derived from the fat of the food, it tends to be of the more fluid acids and contains a larger percentage of olein.

If we compare the formula of glucose, $\text{CH}_2\text{OH}(\text{CH.OH})_4\text{CHO}$, with that of the corresponding fatty acid, caproic acid, $\text{CH}_3(\text{CH}_2)_4\text{COOH}$, we see

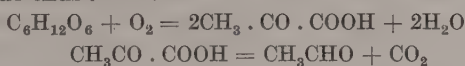
that the conversion involves a considerable loss of oxygen. In order to convert three molecules of glucose, $C_6H_{12}O_6$, into one molecule of stearic acid, $C_{18}H_{36}O_2$, it is necessary to split off 16 atoms of oxygen. That this setting free of oxygen actually occurs in the transformation of carbohydrate into fat is shown by the study of the respiratory exchanges of animals which are rapidly storing up fat at the expense of a carbohydrate food. Thus the marmot, towards the end of summer, eats large quantities of carbohydrate food and very rapidly lays on a thick layer of subcutaneous fat to last it during the winter. If glucose were entirely oxidised in the body, thus



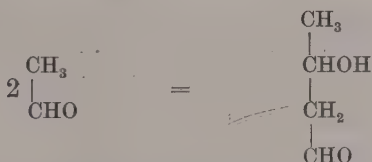
the respiratory quotient would be

$$\frac{6 CO_2}{6 O_2} = 1$$

If, however, oxygen is being set free by the conversion of part of the carbohydrate into fat, this oxygen will be available for the oxidation of other portions of the carbohydrate. The animal will not need to take in so much oxygen from outside for the production of the same amount of carbon dioxide, and the respiratory quotient will rise. Pembrey has shown that under these conditions the respiratory quotient may be as high as 1.5. We cannot assume, however, that the process of conversion of glucose into fatty acids takes place by this simple process of deoxidation. The change is certainly a more complex one, and occurs in separate stages. Glucose breaks up under the action of certain enzymes into two molecules of pyruvic acid, and pyruvic acid can be equally easily converted into acetaldehyde and carbon dioxide thus :



Now aldehyde possesses a marked tendency to undergo polymerisation to aldol,



which, by a simple transposition of oxygen could give butyric acid, or, by oxidation, could give β -hydroxybutyric acid, a substance which occurs during various abnormal conditions of metabolism (*v. also p. 639 et seq.*).

With regard to the glycerol which is a necessary constituent of the neutral fats laid down in the body, there is no difficulty in accounting for its formation from the carbohydrates. By a simple splitting of glucose, we may obtain two molecules of glyceraldehyde, which by reduction is readily converted into the corresponding alcohol, glycerol.

We may conclude that fats are formed by the body with ease from carbohydrates, and that in all probability this change involves a building up of the fatty acid from the lower members by the successive addition of a group containing two atoms of carbon. The whole change, as Leathes has shown (*v. p. 74*), is an exothermic one. For the formation of one molecule of palmitic acid, four molecules of glucose would be required, and 12.5 per cent. of the total energy of the glucose would be set free as heat.

THE FORMATION OF FAT FROM PROTEINS. Among the decomposition products of proteins, the amino-acids take a prominent part.

Of these some, such as alanine, may be converted into carbohydrate in the body, while others, such as leucine and tyrosine, may give rise to aceto-acetic acid. Since carbohydrate is convertible into fat, the former might follow that line, and since aceto-acetic acid is readily convertible into β -hydroxybutyric acid, it seems therefore that these latter might also be built up into fats by the process we have just discussed. For many years, as a result of the investigations of Voit, the proteins were indeed regarded as the chief, if not the sole, source of the fats of the body, and it needed the energetic assaults of Pflüger on this doctrine in 1891 before it could be clearly examined by physiologists.

Let us see what are the grounds for assuming a formation of fat from protein. In the first place, there is a well-known experiment by Voit. A dog was fed with large quantities of lean meat for a considerable time. Voit found that the whole of the nitrogen of the intake was excreted, but that a certain percentage of carbon was retained in the body, and he assumed that it must have been laid down as fat. Pflüger showed that these conclusions were not justified by Voit's results, and were really based on the fact that too high a figure had been assumed for the carbon of the meat. Pflüger proved, moreover, that an animal may be fed in any quantities for weeks on the leanest meat without putting on any fat at all; and, as we have seen, increasing the ration of protein increases simply the nitrogenous and general metabolism of the body. For this last reason a mainly protein diet would usually operate directly against the deposition of body fat, as indeed it is well known to do. However, it is certain that some lower forms of animal life can exist, and form fat on an exclusively protein diet, as Weinland found to be the case for certain fly larvæ, so that the possibility of fat formation from protein is beyond question. Moreover, Atkinson, Rapport and Lusk have recently shown that Voit's main conclusion can be substantiated when sufficiently large amounts of protein are given to a well nourished resting animal kept in a warm environment.

Although we must assume that the healthy body does not normally form fat from protein, there are some pathological conditions which seem at first to tell in favour of such a conversion. Thus during certain diseases, such as diphtheria, pernicious anæmia, and as the result of poisoning by phosphorus, the majority of the organs of the body undergo acute fatty degeneration. The liver cells are studded with fat granules, and this was long interpreted as due to a direct conversion of protein into fat. More exact analyses have shown that, during fatty degeneration, the total fat in the body is not increased. Thus one observer took 124 pairs of frogs and poisoned one of each pair with phosphorus. The animals were then killed, and the whole of them analysed. The difference in the content of fat between the poisoned and unpoisoned animals fell within the limits of experimental error, so that there had been no increase in the fat of the body as the result of the poisoning. In some cases there is also a deposition of fat in the liver cells due to the immigration of the fat from other parts of the body. This is shown by the fact that the composition of the fat in the degenerated liver varies according to the composition of the fat in the rest of the body. In fatty degeneration two processes are at work: one is the immigration of fats from other parts of the body; the second, and probably the more important one, is a change in the relation of the fat to the protoplasm of the cell.

It was long stated that the fat of milk was not increased by feeding with fats, but only by feeding with proteins. More recent researches have given contrary results. The dependence of the composition of milk fat on the composition of the fat present in the body or administered in the food is shown by the fact that cows fed on oilcake may produce a butter which is useless for commercial purposes owing to its low melting point. In one experiment, when a cow was fed on linseed oil, the iodine number of the milk fat rose from 30, its normal figure, to 70.4. After the introduction of iodine fat subcutaneously, iodine fats are found in the milk. In another experiment a bitch, which had been fed with mutton suet and had deposited in its tissues a fat of high

melting point, produced a milk the iodine number of which was the same as that of the mutton suet. In this case the fat of the milk had evidently been derived from the tissues, since during the lactation the animal was being fed on meat which was poor in fat. The same dependence of fatty secretion on diet has been found in geese, where the composition of the oil secretion of the feather glands has been altered by giving unusual fats, such as sesame oil, with the food.

We must conclude that, though it is chemically feasible, in actual fact the protein of the food does not usually give rise to fat in the body. A nearer consideration of the composition of the proteins, taken in connection with our discussion as to the mechanism by means of which the fat is built up in the body, may help to account for this fact. The fatty acids formed by the disintegration of proteins are chiefly the lower acids of the series, such as acetic and propionic, which would undergo rapid oxidation in the body, and the 6-carbon acid derived from leucine is not the normal acid, but is a branched chain, viz. isobutyl-acetic acid.

THE UTILISATION OF FATS IN THE BODY

The constant presence of fat, and bodies allied to fat, in protoplasm, from whatever source obtained, suggests that these substances play an essential part in vital phenomena. The direct utilisation of fat for the needs of the body is also indicated by the results of experiments on man and the lower animals. After a few days' starvation, the body may be regarded as practically free from stored carbohydrate. The sole source of the energy which is evolved under these circumstances must be fats and proteins, and it is possible by an estimation of the nitrogen output to determine the exact fraction of the total energy evolved which is to be ascribed to protein metabolism. Thus in the case of Cetti, the professional faster, it was found that the nitrogenous metabolism per unit of body weight remained fairly constant between the fifth and tenth days of starvation, and corresponded to an average of 1 gramme of protein per kilo. body weight daily. In order to oxidise this amount of protein nearly 2 grammes of oxygen would be required in the twenty-four hours, i.e. about 1 c.c. per minute. Cetti's total oxygen consumption was at the rate of 5 c.c. per kilo. per minute, so that four-fifths of the oxygen absorbed was required for the oxidation of non-nitrogenous substances, and these, as we have seen, could only have been fats. In animals with a large store of fat the proportion of the energy obtained at the cost of the fats may be still greater. In dogs, Rubner and Voit reckoned that only 10 to 16 per cent. of the total energy was derived from proteins, the rest being obtained from the oxidation of fats.

The oxidation of fats supplies energy not only for the production of heat but also for the performance of mechanical work. Fat is found as a normal constituent of all muscle fibres, and the amount of this substance is greater in proportion to the activity of the muscles concerned. Thus the ever-active heart muscle and the red muscles of the diaphragm contain larger amounts of fat than the pale voluntary muscles which have to undertake only short periods of activity. In the human heart muscle 15 per cent. of the solids are soluble in ether, and more than one-half of the ether extract is composed of fat, and is sufficient to supply the energy of the contracting heart for six or seven hours' work. Yet we have no evidence that this fat can be used as the immediate source of the energy of the muscular contraction. As we have already seen (p. 175), the chemical changes accompanying muscular activity are centred mainly, if not entirely, round glycogen. Hill and Furusawa have shown that, even in individuals fed on a preponderatingly fat

diet, the respiratory quotient during exercise is unity. But after the exercise, or if hard exercise is prolonged, the quotient falls, and this is interpreted as indicating that the muscle (and liver) are replenishing their stores of glycogen at the expense of fat. How and where this conversion takes place, and whether it can be effected by the muscles themselves, we have at present no means of determining.

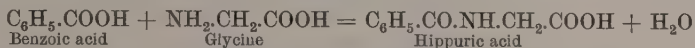
In prolonged moderate exercise the respiratory quotient must therefore be the same as during rest, provided that the diet remains the same. The respiratory quotient under these conditions depends merely on the nature of the food oxidised, and it makes no difference what intermediate changes take place, such as that of fat to carbohydrates or *vice versa*, provided that all the food used finally undergoes complete oxidation. This is well shown in the following Table, in which the oxygen consumption and respiratory quotient are compared in a man resting and working on three different diets, one principally fat, one principally carbohydrate, and the other principally protein :

Diet principally	Resting		Working		kg. m. of work done	Per kg. m. of work	
	c.c. oxygen used per min.	Resp. quotient	c.c. oxygen used per min.	Resp. quotient		c.c. oxygen used	Cal.
Fat	319	0.72	1029	0.72	354	2.01	9.39
Carbohydrate	277	0.90	1029	0.90	346	2.17	10.41
Protein	306	0.80	1127	0.80	345	2.38	11.35

The changes in the fat molecules, which are involved in the utilisation of their energy, are still to be determined. The energy of fat is available only on its oxidation. The transformation of fats into fatty acids or glycerol, or the synthesis of fats from aldehydes or from carbohydrates, which we have discussed in the previous section, do not involve any large changes of energy. Weight for weight, butyric acid with its 4 carbon atoms has practically the same heat value as stearic acid with its 18 carbon atoms, or stearin with its 57 carbon atoms. We have, therefore, to determine what changes the fatty acid molecule undergoes before it is brought into a condition in which it may be oxidised and set free the energy required for the purposes of the body. The general tendency of metabolic research of recent years is to show that the living cell is in a position to effect all changes, which do not involve a large evolution or absorption of energy, in either direction. In the plant cell, at any rate, the fatty acids may be converted into amino-acids, or the latter may be deaminised. If, therefore, fats are constantly being made from carbohydrates or from the lower molecules such as aldehyde, it seems possible that the same change may go on in a reverse direction when fats are broken down previous to oxidation.

Although we cannot trace out in the animal body the stages in the breakdown of a large fatty acid such as stearic acid, we have evidence that the breakdown, like the building up, of fats occurs by two carbon atoms at a time. When, in the process of breaking down, a fat finally arrives at the four- or two-carbon stage, it is quickly oxidised and lost ; similarly, if acetic acid or ethyl alcohol be administered in small quantities, they are entirely oxidised. If, however, these bodies be attached to a benzene ring, and be administered as a phenacetic acid or phenylethyl alcohol, they are excreted in the oxidised form of phenaceturic acid, which is simply a combination of

phenacetic acid with glycine. In the same way benzoic acid or benzyl alcohol are excreted in the form of hippuric acid, thus :



Phenacetic acid, $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{COOH}$, is excreted as phenaceturic acid or phenacetyl glycine, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\text{COOH}$. In each case the fatty side chain is protected from further oxidation by its attachment to the benzene ring and by the tacking on of the glycine molecule.

With phenyl propionic acid two carbon atoms of the side chain are oxidised, and the remaining benzoic acid excreted as hippuric acid. Phenyl-butyric acid undergoes a similar change, leaving phenyl acetic acid, which is excreted as phenacetyl glycine. If phenyl valerianic acid be given, four carbon atoms are oxidised away ; benzoic acid is left and appears in the urine as hippuric acid. In each case the oxidation of the side chain occurs by two carbon atoms at a time, and it seems probable that a similar change will take place in the ordinary fatty acid, the last stages, in the absence of any protective ring compound, being oxidised like the earlier groups and therefore not detectable in the excretions.

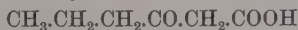
Evidence in the same direction is afforded by certain cases in which the oxidative power of the body for fats is inadequate, either by reason of morbid changes in the oxidative powers of the body, or as the result of what we may call an overstrain of the fat-oxidising powers. Such a condition is found in '*ketosis*,' such as occurs in starvation, in exclusive fat feeding, or in the end stages of diabetes. Aceto-acetic and β -hydroxybutyric acids, and acetone ('*acetone bodies*'), are found in the urine in this condition. Thus in one experiment a healthy man took as his sole diet for five days a daily ration of 250 grammes of butter, 200 grammes of oil and a little wine. The result was an intense ketosis, such as occurs only in the severest cases of diabetes, '*acetone bodies*' being found in the urine in large quantities. On the last day of the experiment these acids caused so much of the nitrogen in the urine to appear as ammonia that, of the 5.8 grammes total nitrogen excreted, only 2.7 grammes were in the form of urea, while 2.1 grammes were present as ammonia.

If, during a period of starvation in man, a day is interpolated on which 100 grammes of protein are taken, the amount of acetone excreted falls below that obtained on the other days when the individual is living chiefly at the cost of his own fat. If sufficient carbohydrate is given, the acetone bodies practically vanish. These facts indicate that the chief source of the acetone bodies is the fat of the food or of the body. The condition of ketosis is more easily brought about by ingestion of butyric acid than of the higher acids such as palmitic or stearic, suggesting that whatever fatty acid is given it is reduced to butyric or β -hydroxybutyric acid before its final destruction, and that in the condition of ketosis it is merely the last stages of this oxidation which are at fault. We are thus justified in concluding that the oxidative breakdown of fats occurs mainly by an oxidation in the β position.

If we take, for instance, the 6-carbon stage :



The first change which probably occurs is the oxidation :



A further change is the complete oxidation of the last two groups and the production of butyric acid :



This then again undergoes oxidation in the β position, with the production of aceto-acetic acid :



which, by reduction, may be converted to β -hydroxybutyric acid,



In the normal individual, this last stage undergoes complete oxidation, both hydroxybutyric acid and aceto-acetic acid given to a healthy person being completely destroyed in the body. It is only under the abnormal conditions which we have mentioned above that they escape complete oxidation and are excreted unchanged in the urine.

Dakin has shown that similar products are formed by oxidation of the ammonium salts of the fatty acid by hydrogen peroxide. Another path for oxidation of the fatty acids is indicated by the work of Hurtle on butyric acid, and of Clutterbuck and Raper on various higher acids. They find that on oxidation with hydrogen peroxide not only the β , but the γ and δ , and perhaps also the α groups, are oxidised, and that an important product of the reaction is succinic acid, $\text{COOH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COOH}$.

THE QUESTION OF THE FORMATION OF SUGAR FROM FAT

The evidence that the energy of muscular contraction is derived entirely from carbohydrate requires, as a logical necessity, the possibility of the conversion in the body of fat into carbohydrate. And yet the evidence for this conversion is by no means satisfactory. Such a conversion is of normal occurrence during the germination of fatty seeds; these are found to absorb oxygen and to give off carbon dioxide, but much less carbon dioxide is given out than would correspond to the volume of oxygen absorbed.

The same change in the relation of oxygen intake to carbon dioxide output is found under certain conditions in animals. During hibernation, as Pembrey has shown, the marmot has a very low respiratory quotient, which may not be greater than 0.3 or 0.4. This means that the animal takes in more oxygen than the carbon dioxide which it gives out, and this intake of oxygen can be so marked as to cause an appreciable increase in the weight of the animal. This retention of oxygen can be explained only by assuming that there is going on in the body a conversion of substances containing a small amount of oxygen into substances containing a larger amount of oxygen; such a conversion as that of fats into carbohydrates. Just as the high respiratory quotient obtained from a marmot during the period of putting on fat was shown to be associated with a conversion of carbohydrate into fat, so does the abnormally low quotient obtained during hibernation suggest the reverse change of fat into carbohydrate.

The same conversion has been alleged to take place in certain cases of diabetes. In many cases when the diabetic animal is living on a purely protein diet, a uniform ratio has been found to exist between the glucose and the nitrogen excreted, *i.e.*,

$$\frac{G}{N} \text{ generally equals } 2.8.$$

In certain other cases a constant G : N ratio of 3.65 has been found. The former represents a conversion of 45 per cent., the latter of 58 per cent. of protein into sugar. In a few cases, however, even during complete starvation, the ratio G : N has been found to be much greater than that given above and to amount to as much as 10 or 12. These animals are stated to be practically free from carbohydrates, so that the sugar excreted in the urine can come only from the breakdown of proteins or fats. It is

impossible to get from a protein molecule ten times as much dextrose as corresponds to the nitrogen, and Pflüger concludes that, in cases where such a high G : N ratio exists, the dextrose must have been derived by a conversion of the fats of the body. This conclusion, though not universally accepted, would bear out the general statement made above: that in the living body practically all the chemical changes are reversible, and that the living cell can so regulate the conditions of the reaction that the reversible reaction becomes practically complete in either direction, the direction being determined by the needs of the body at the time.

Accepting this generalisation, the chemical mechanism by which fats are converted into carbohydrates is probably the reverse of that by which carbohydrates are changed into fats. The 2-carbon group split off from the large fatty molecules would be utilised for the building up of the sugar molecule. We know that such a synthesis can take place from such simple groups as formic, glycollic, or glyceric aldehyde. Another path would be by the conversion of the fat into succinic acid, which is easily converted in the tissues into fumaric, and then to malic, acid, and so to glucose. Though it is impossible to deny to any cell of the body the power of effecting the conversion of fats into carbohydrates, or carbohydrates into fats, the chief centre for such conversions is probably the liver. During starvation, and in diabetes, the liver is found to be heavily infiltrated with fat. As already explained, the fat of the liver, like that of other tissues, contains a high proportion of unsaturated acids, largely in the form of phospholipides. It is suggested that the desaturation of the fat with which the liver becomes filled under conditions in which the fat utilisation is enhanced, is a preparation for its further rapid break-up into small and reactive molecules, some of which might undergo final oxidation directly, while others are converted into carbohydrate. It is significant that in the course of fatal diabetes, in which the fat almost disappears from the body, the liver is the only organ which retains its weight unchanged. During this disease there has been an enormous amount of work done in the conversion of proteins, and possibly of fats, into carbohydrates which could not be utilised by the body; and the large size of the liver at death suggests that the work of transformation has been performed by this organ.

4.—CARBOHYDRATE METABOLISM

All the carbohydrates which are taken in with the food are ultimately transformed in the alimentary tract, or in its walls, into the three monosaccharides, glucose, fructose and galactose. These three, together with mannose, are the only sugars which are directly assimilable by the higher animals. A consideration of their structural formulæ suggests that they might be easily interconvertible. This conversion actually takes place in watery solution. If a solution of any one be left for some months, it will be found to contain all three at the end.

Since these monosaccharides must enter the blood in large quantities during the absorption of a heavy carbohydrate meal, one would expect to find a much greater proportion in the blood after such a meal than during a period of starvation. The amount of reducing sugar in the blood is, however, practically constant, and only varies between about 0.1 and 0.2 per cent.

Searching for the origin of this constant proportion of reducing sugar, Claude Bernard found that the blood of the hepatic vein in a fasting animal contained more sugar than the blood taken at the same time from the portal vein. If the liver, taken from an animal which has been dead for some

time, be extracted with water, the extract is found to contain a large quantity of reducing sugar (glucose). If however it be removed immediately the animal is dead, its vessels washed out with ice-cold saline fluid, and it be then cut up and thrown into boiling water, ground and extracted, the extract, after separation of the coagulable proteins, contains hardly a trace of sugar, and no more than is present in the blood. The fluid is opalescent; and Bernard found that this opalescence was due to the presence of a substance which he called *glycogen*, *i.e.* the sugar-former.

After a carbohydrate meal, glycogen may be present in very large amounts in the liver, up to 12 per cent. of the weight of the fresh liver. When pure, it forms a snow-white powder, tasteless and odourless, with a formula $C_6H_{10}O_5$. Like starch, it is hydrolysed by the action of acids and superheated water, or of amylolytic enzymes, into dextrins, maltose and finally glucose. It gives with iodine a mahogany-red colour, which disappears on boiling but returns again on cooling.

The large amount of sugar found in the liver which has been left in the body is due to the conversion of glycogen into glucose. That it is really an enzyme action is proved by the fact that the liver may be dehydrated with alcohol, dried and powdered, and kept for months in this condition without any alteration occurring in the glycogen. If, however, the coagulated liver be mixed with water and allowed to remain at the temperature of the body for some hours, the glycogen is found to disappear and give place to glucose.

FORMATION OF GLYCOGEN. In order to obtain a large amount from the liver, the animal is fed twelve to twenty-four hours previously on a meal which is rich in carbohydrates. Only those carbohydrates which we have mentioned as directly assimilable, *i.e.* which will give rise in the alimentary tract to mannose, glucose, fructose or galactose, will cause an increased formation of glycogen.

Glycogen can also be formed from the proteins of the food or from the products of their disintegration, the amino-acids. By means which we shall consider shortly, it is possible almost to free the liver of animals from glycogen: if such animals be fed on a diet of washed fibrin or of pure caseinogen, or even on the ultimate products of pancreatic digestion of proteins (containing, therefore, only amino-acids), and be killed shortly afterwards, the liver is found to contain more glycogen. It does not seem to be possible for the liver to store glycogen out of fats. At any rate, that is the interpretation which is generally placed on experiments on feeding with fats. In these experiments it is found that, if fats be administered to an animal after the liver has been almost freed from glycogen, although the liver may store up fats it does not store up any glycogen.

If an animal be starved, the glycogen gradually disappears from the liver although, even at the end of ten or twelve days' complete deprivation of food, small traces of glycogen may still be found in this organ. Even if starvation be combined with hard work, its liver never becomes quite free from glycogen. The same reduction of glycogen may be produced by any means which evoke an increased muscular activity, *e.g.* poisoning with strychnine. Of the various reserve materials which are available, the carbohydrate is the first to be called upon to meet the increased needs of the tissues during functional activity, such as muscular work or greater heat production. Thus the glycogen rapidly diminishes in the liver of a rabbit which has been immersed in a cold bath.

The glycogen of the liver represents a reserve material analogous to the reserve carbohydrates stored up as starch in different parts of plants. When the blood is loaded with carbohydrates, a considerable proportion is

laid down as the inert polysaccharide, glycogen. As soon as the supply of sugar to the blood is withdrawn, the tissues continue to use the sugar of the blood, which is made up at the expense of the glycogen in the liver. In every liver cell, therefore, a twofold process is always going on: a building up of glycogen by the activity of the liver cells, and a breaking-down of glycogen under the action of the enzyme in the liver cells. Which of these two processes preponderates depends, in the normal animal, on the concentration of sugar in the blood which is circulating through the organ.

On account of the importance of glycogen as a reserve material, it is produced and stored up in almost all growing tissues, to be utilised in their subsequent development. Thus it is found in large quantities in the placenta during a certain period, in foetal muscles and in various other situations. It is found in yeast, in oysters and in the muscles of the body generally. In foetal muscles it may amount to as much as 40 per cent. of the total dried solids. The glycogen of the adult muscle is utilised during muscular work, and diminishes in amount with activity of the muscle. In adult muscles it never reaches anything like the percentage which is found in the liver. The average amounts in the different tissues are given by Schöndorf as follows:

	Maximum per cent. of fresh tissue	Minimum per cent. of fresh tissue
Liver	18.69	7.300
Muscle	3.72	0.720
Heart	1.32	0.104
Bone	1.90	0.197
Intestines	1.84	0.026
Skin	1.68	0.090
Blood	0.0066	0.0016

THE UTILISATION OF SUGAR IN THE BODY. The only sugar so far identified in normal blood is glucose, which is present in human blood in amount varying from 0.08 per cent. to 0.18 per cent.

A fact of the greatest interest is that the sugar content of the blood is not absolutely constant; the variations, though not usually great, are nevertheless of the utmost importance. The chief cause of alteration of the blood sugar is the ingestion of carbohydrate food, for the liver does not at once remove the whole of the absorbed carbohydrate which is passed to it in the portal blood.

The effects of ingestion of carbohydrate are best seen in the determination of what is known as the *blood-sugar curve* (Fig. 236). For this purpose the fasting level of the blood sugar is determined, and then 50 or 100 grammes of glucose dissolved in water are taken by the mouth. Samples of blood are drawn from the finger or ear for sugar estimation each half hour, for three hours. In most normal people the fasting blood-sugar level is about 0.10 per cent.; within thirty minutes after taking glucose this has risen to about 0.18; in one hour the amount has begun to fall, and at the end of one and a half to two hours after the glucose meal, the blood sugar has returned to normal again, or may even be a little below. If insoluble carbohydrates, such as starch, be taken instead of glucose, the rise is often smaller, and of slightly longer duration, owing to the relatively slow digestion and absorption of the products.

Diminution of the sugar content of the blood much below 0.07 per cent. is attended with severe symptoms, and finally leads to the death of the

animal. This condition of *hypoglycæmia* may be brought about by the injection of insulin, a hormone derived from the islets of the pancreas. In the rabbit, a reduction of the blood sugar to about 0.045 per cent. causes severe convulsive seizures, followed by coma, a fall of temperature and death from respiratory failure. In man, subjective symptoms are noticed when the blood sugar falls to 0.075 per cent. These are extreme hunger and a sense of fatigue, with anxiety. Vasomotor phenomena such as pallor or flushing are common, and there is general sweating. As the blood sugar falls still further, mental disturbances, delirium and finally profound coma supervene. It is evident that the small percentage of sugar always present in blood is essential for the maintenance of the normal functions of the central nervous system.

That sugar is being used up in all the processes of the body is shown by the immediate alteration in the respiratory quotient which occurs when the food is changed from a mixed diet to one consisting mainly of carbohydrate. An important factor in the maintenance of a constant sugar content in the blood is the reversion of the stored-up glycogen of the liver into sugar. The glycogen is not, however, the sole source of the sugar,

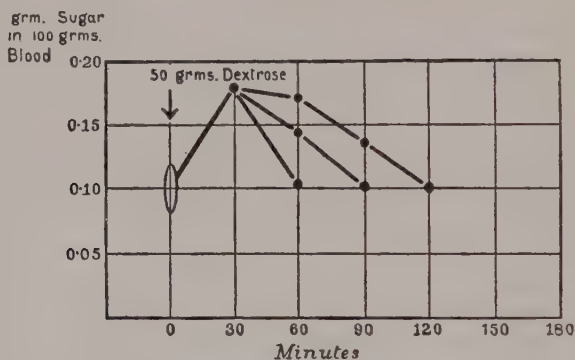


FIG. 236. Limits of Blood-sugar Curve in Normal Persons, after 50 grammes glucose.
(G. GRAHAM.)

since in complete starvation the sugar content of the blood remains constant even after the last traces of glycogen have disappeared from the liver. If the liver be cut out of the body or removed from the circulation, during the few hours that the animal survives there is a steady diminution in the blood sugar, pointing to the liver being, in the fasting animal, the chief, if not the sole, source of the blood sugar. In some animals, *e.g.* the carnivora, it would seem that the liver can continue to supply sugar to the blood on a diet which includes only proteins and fats; and we have already seen that in such animals glycogen itself can be stored up at the expense of protein. It is doubtful whether a perfectly normal existence is possible in man in the total absence of carbohydrates from the food, though there is no doubt that in the northern races, *e.g.* the Eskimos, the amount of carbohydrate consumed is very small in comparison with the fats and proteins. During muscular exercise the increased output of energy is associated with a corresponding increase in the consumption of carbohydrate in the contracting muscles. We must conclude that sugar is being normally released by the liver into the blood stream, to maintain the proportion of this substance in the blood at a certain level, and that the sugar is as constantly being taken up and converted into glycogen in the muscles, to replace that used up during contraction. The venous blood flowing from a contracting

muscle contains less sugar than the arterial blood flowing to the muscle. A similar consumption of glucose occurs in the isolated contracting mammalian heart. A heart, fed with blood and performing a normal amount of work, may use about 4 mg. sugar per gramme of heart muscle per hour.

GLYCOSURIA

Normal urine has been often stated to contain a small proportion of sugar. Recent investigations have shown however that the reducing substances present in small quantities are not glucose. The term *glycosuria* is not employed unless sugar appears in quantities large enough to give a reaction with Fehling's solution or with the phenyl hydrazine test. Such a condition may easily be brought about by the injection of sugar subcutaneously or intravenously. It is then found that any trace of the disaccharides, cane sugar or lactose, introduced in the circulation, is excreted in the urine. A rather larger quantity of maltose may be injected slowly without appearing in the urine, since the blood serum contains an enzyme, maltase, which converts the maltose into glucose. Glucose, fructose, mannose or galactose, if introduced slowly into the circulation, are stored up as glycogen in the liver. If, however, the sugar in the blood rises above about 0.18 per cent., the sugar (generally glucose) appears in the urine. When this condition of *hyperglycæmia* (excess of sugar in the blood) is set up, the concentration of the sugar in the urine is much greater than that in the blood. If the sugar in the blood amounts to 0.4 per cent. the urine may contain from 2 to 7 per cent. of glucose.

The occurrence of glycosuria depends upon two things: (1) The sugar content of the blood; (2) the renal sugar threshold. When glycosuria occurs it means that the blood sugar has risen to a value higher than the renal threshold; consequently, glycosurias may be due to one of two classes of cause: first, to an abnormally high blood sugar; second, to an abnormally low kidney sugar threshold. The latter type, called *renal glycosuria*, has no further interest for us here, apart from the importance of distinguishing between it and the other forms which are met clinically and which are more serious.

(1) **ALIMENTARY GLYCOSURIA.** A state of hyperglycæmia may be induced by the administration of abnormally large quantities of glucose by the mouth. In a healthy individual the amount has greatly to exceed 100 grammes in order that any shall appear in the urine. In certain individuals the power of assimilating glucose may be deficient, so that an alimentary glycosuria may be caused by any over-indulgence in carbohydrate food. In the healthy person it is hardly possible to produce glycosuria by the administration of carbohydrates, since the liver can store up the excess of glucose as fast as it is absorbed into the blood stream.

(2) **DIABETIC PUNCTURE.** It was shown by Claude Bernard that puncture of the floor of the fourth ventricle in rabbits is often followed immediately by an excessive secretion of urine containing sugar. The glycosuria may last from twenty-four to thirty hours. If at the end of this time the animal be killed, the liver is found to be free from glycogen. A sample of blood taken during the height of glycosuria may contain from 0.3 to 0.4 per cent. of sugar. In order that the experiment may succeed it is important that the animal be previously well fed. If the puncture or 'piqûre' be carried out on an animal whose liver has been freed by any means from glycogen, no glycosuria is produced. It is evident that the effect of the puncture has been to cause a rapid conversion of the glycogen previously stored up in the liver into glucose. The glucose so formed escapes

into the blood, and the excess is immediately excreted by the kidneys, together with an increased amount of water. A similar temporary hyperglycæmia and glycosuria may be brought about by fright, struggling, or the administration of anæsthetics; but the effect is absent if both splanchnic nerves have been previously divided above the suprarenals. It has been shown (Elliott, Cannon) that all these conditions are associated with an increased discharge of adrenaline, from the medulla of the suprarenals, into the circulation. Since the injection of adrenaline itself causes a condition of glycosuria similar in all its limitations and aspects to 'puncture diabetes,' it is now generally believed that the two conditions are identical, and that the diabetic puncture acts through the splanchnic nerves on the suprarenals, setting free adrenaline, which passing to the liver causes a rapid 'mobilisation' of the stored-up glycogen, and a consequent hyperglycæmia and glycosuria, lasting as long as the glycogen store holds out.

(3) **PHLORIDZIN GLYCOSURIA.** Phloridzin is a glucoside extracted from the root cortex of the apple tree. It may be decomposed into a sugar and phloretin. When phloridzin or phloretin is administered by the mouth or subcutaneously, it gives rise to glycosuria. The urine may contain from 5 to 15 per cent. of glucose. The glycosuria induced in this way differs from the forms already described in the fact that it is not due to hyperglycæmia. The blood sugar is, in fact, diminished. In this respect, therefore, the condition resembles renal glycosuria, and apparently differs from it only in degree, inasmuch as the renal threshold is not lowered, but abolished. This is due to a specific effect of the drug upon the kidneys. If cannulæ be placed in the two ureters so as to collect the urine from each kidney separately, and a small dose of phloridzin be then injected by a hypodermic syringe into the left renal artery, the urine flowing from the left ureter will in two minutes be found to contain sugar, while the urine from the right kidney will not contain any sugar for another five or ten minutes. The effect therefore is rapidly to drain off sugar from the blood. In order to maintain the sugar content of the blood at its normal height, the liver must manufacture fresh sugar to take the place of that lost by the kidneys. In the first instance the liver will utilise its stored-up glycogen for this purpose. If a dose of phloridzin be given to each of two animals, and one animal killed as soon as the excretion of sugar is coming to an end, its liver will be found free from glycogen. If now a second dose of phloridzin be given to the other, which may be regarded as free from glycogen, glycosuria is produced as before, and the excretion of sugar can be provoked indefinitely by repeated administration of the drug. So long as sufficient food is given, including carbohydrates, the loss of sugar does not entail any increase in the destruction of the tissues; but if the drug be administered to starving animals, the waste of sugar has to be made good at the expense of material other than carbohydrate. In phloridzin glycosuria, therefore, we can readily study the process by which the body forms sugar, and it has accordingly proved a very valuable means of investigation.

The readiest source of the sugar excreted under these circumstances is the protein of the tissues. The nitrogen excreted in the urine rises in amount in proportion to the quantity of sugar excreted, and there is a constant ratio between the amounts of nitrogen and of sugar excreted in the urine. In different experiments this ratio G : N varies from 2.8 : 1 to 3.6 : 1. If meat be administered to such starving animals with glycosuria, the G : N ratio does not alter; the amount of nitrogen in the urine increases, but the sugar increases in the same proportion. The sugar must therefore be derived from protein, *i.e.* from the amino-acids of which the protein is composed. It has been shown by Lusk, Embden, and Dakin that the following amino-acids

yield large amounts of glucose when administered to a phloridzinised animal: glycine, alanine, serine, cystine, aspartic acid, glutamic acid, ornithine, proline and arginine. We must assume that these amino-acids, produced in digestion or by the autolysis of the tissues, undergo deamination and that the sugar is formed by a process of synthesis from the ketonic acids thereby produced. On the other hand leucine, tyrosine and phenyl alanine give no increase in the output of sugar. It is, however, just these amino-acids which seem to follow the line of fat metabolism, since they are converted into aceto-acetic acid when perfused through a dog's liver; and the administration of fats to a phloridzinised dog is also without effect on the sugar excretion. It is this fact which has led Lusk and others to deny the possibility of conversion of fats to carbohydrates taking place at any time in the body. The drain of sugar from the organism determined by the action of phloridzin on the kidneys thus necessitates a continued breakdown of the nitrogenous tissues of the body in the effort to maintain a normal supply of sugar to the tissues, and unless excessive feeding be employed the animal must waste. The great increase in the nitrogenous output resulting from the condition of phloridzin diabetes is shown in the following Table (Lusk):

	GOAT			Dog		
	G	N	G : N	G	N	G : N
Fasting	—	3.72	—	—	4.04	—
Fasting	—	3.71	—	—	4.17	—
Fasting and diabetic	20.33	4.90	4.15	63.55	12.66	5.02*
Fasting and diabetic	26.08	8.83	2.95	65.30	18.76	3.38
Fasting and diabetic	23.39	8.06	2.90	65.84	18.57	3.54
Fasting and diabetic	19.01	6.84	2.78	64.60	17.29	3.74

The constant drain of sugar will in time involve a relative carbohydrate starvation of the tissues, which will make good their energy requirements as much as possible, at the expense of protein and fat. The administration of meat will diminish the fat metabolism to a certain extent, but since it does not alter the G : N ratio, it would appear that the latter does not depend in any way on the quantity of fat undergoing oxidation. This is shown in the following respiration experiment (Mandel and Lusk) on a dog with phloridzin glycosuria, in which the metabolism during starvation and after ingestion of meat was determined :

	G : N	Calories from protein	Calories from fat	Calories total.
Fasting	3.69	80.2	274.4	354.6
300 grammes meat	3.55	161.9	261.7	423.6

An enormous waste of energy is involved in such a constant loss of sugar, and it is not to be wondered at that the nitrogenous metabolism may be increased three- to five-fold as a result of the artificial induction of carbohydrate loss.

The carbohydrate starvation has other deleterious effects, since we have

* The high G : N ratio on the first day is evidently due to the conversion of the glycogen still present in the body.

evidence that a certain amount of carbohydrate food is a necessary condition for both fat and protein metabolism. The necessity of carbohydrate for the assimilation of protein is brought out in an experiment by Cathcart. It has long been known that carbohydrate administration has a sparing effect on protein metabolism. If an animal or man be starved, the nitrogenous output sinks to a certain level and there remains practically stationary. If now pure carbohydrate food be administered sufficient to meet the energy requirements of the animal or man (about 35 Calories per kilo.), there is at once a rapid drop in the output of nitrogen and therefore in the protein waste of the tissues. Fat has a much slighter or no sparing effect on the nitrogenous metabolism. Indeed in certain experiments by Cathcart the administration of fat caused an actual rise in the nitrogenous output.

The importance of carbohydrates is borne out by the results of feeding animals with proteins which have been digested with pancreatic juice until the biuret reaction has disappeared. After Loewi had shown that it was possible to maintain nitrogenous equilibrium in dogs with such a digest, Lesser was unable to confirm his results. But it was pointed out that the essential difference between the two observers was that Loewi gave an abundant supply of carbohydrates with the digest, while Lesser omitted carbohydrates altogether and administered fats and protein digest alone.

The evidence that the carbohydrates play a necessary part in the metabolic history of fats has already been mentioned (*v. p.* 639). We have seen that, in the absence of carbohydrates, the last stages in the oxidation of fats make default, so that the acetone bodies accumulate in large quantities and are excreted in the urine. The appearance of these keto-acids and acetone is spoken of as *ketosis*, and sugar is said to be *antiketogenic*. The function of sugar in this respect may be due to a reaction taking place between one of the 'acetone bodies' and glucose itself or some product of decomposition or oxidation of glucose, such reaction being essential for the complete oxidation of the acetone bodies. This view is supported by the definite relationship between the amounts of carbohydrate and fats which is necessary to prevent ketosis. It has been shown that no ketosis occurs when one molecule of sugar is oxidised in the body for each molecule of the aceto-acetic acid which may be formed from the fats (or a portion of the proteins) of the food. When the proportion is only 1 to 2, there is always some ketosis, and when the proportion of potential aceto-acetic acid to glucose exceeds 2, the whole excess is excreted as ketone bodies. This relationship is of practical importance in the dieting of diabetics.

Shaffer has shown that, when one molecule of sugar is mixed with two molecules of aceto-acetic acid in strongly alkaline solution containing hydrogen peroxide, the whole mixture undergoes rapid and complete oxidation.

Not only does the excretion of ketone bodies involve a loss of energy to the body, but these organic acids require bases for their neutralisation, and as we have already learned, when these are no longer present in sufficient quantity, the acids will be excreted in combination with ammonia. If the condition of carbohydrate starvation be continued, this mechanism of neutralisation is insufficient, and the phenomena of acidosis, *viz.* dyspnoea and coma, ensue as the death of the animal approaches.

Another effect of continued administration of phloridzin is fat infiltration of the liver. This is merely a result of the carbohydrate starvation. The liver seems to be able to act as a storehouse either of fat or of carbohydrate, so that there is an inverse ratio between the amount of glycogen and the amount of fat stored up in the liver at any given time.

(4) **PANCREATIC DIABETES.** Von Mering and Minkovski found that total excision of the pancreas gives rise to a rapidly fatal diabetes, which is

closely similar to the severer cases of diabetes in man. The operation is followed in a few hours by the appearance of a large amount of sugar, 5 to 10 per cent., in the urine. The glycosuria persists; the animal rapidly wastes, and finally dies at the end of a week or so from diabetic coma. The condition of diabetes observed under these circumstances has nothing to do with the presence or absence of the pancreatic secretion into the intestine, since ligation of the ducts of the pancreas, or obstruction of the ducts by the injection of melted paraffin, does not give rise to diabetes, although these procedures are followed by atrophy of the secretory part of the gland.

We thus see that the pancreas has a two-fold function: the secretion of a digestive juice into the intestine, and the exercise by some means or other of an influence on general metabolism, the absence of which

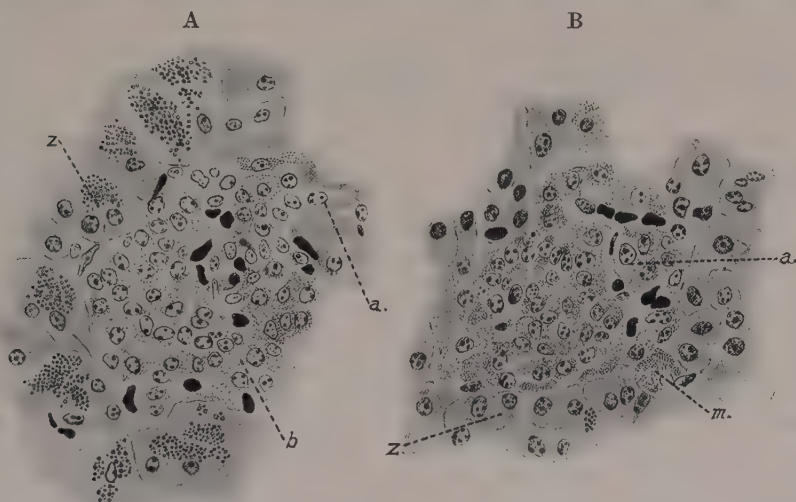


FIG. 327. (A) and (B) show an Islet with the surrounding Tissue in a resting Gland (A) and after Exhaustion with Secretin (B).

In (A) the secreting acini are charged with zymogen granules. In (B) these have entirely disappeared. On the other hand no change is noticeable in the cells of the islet. In the latter the granular cells are the β cells, and the clear hyaline cells are the α cells, (m) showing what are called Minkowski granules. The granulation of this cell is regarded by Bensley as due to postmortem changes.

is followed by the supervention of diabetes. Corresponding with this two-fold function, two kinds of structures are present in the gland, the secreting acini and the islets of Langerhans. These latter, though arising in connection with the ducts, are solid masses of cells and have no communication with the lumen of the ducts. According to Bensley and Lane, the stainable islet cells may be divided into two varieties, which have been given the name of α and β cells, according as their granules are fixed respectively by alcoholic or watery solutions. It has been shown, both by Bensley and by Homans, that these cells undergo no alterations when the gland is excited to secrete by the injection of secretin (Fig. 327). On the other hand, if four-fifths of the pancreas be removed, the remaining part may gradually become inadequate to prevent diabetes; and Homans has shown that, when under these circumstances diabetes supervenes, the granules disappear from the β cells. Changes have also been found in the islets of Langerhans in fatal cases of diabetes in man.

INSULIN. These facts led physiologists to believe that the influence of

the pancreas in preventing diabetes depended on the formation of a hormone in the islets of Langerhans, and that this hormone was in some way necessary for the normal metabolism of carbohydrates. Already in 1916 Schafer had proposed for this hypothetical hormone the name of insulin, but it was not till 1922 that Banting and Best, in Macleod's laboratory, succeeded in extracting the hormone in a concentrated form from the normal pancreas, and in showing that, by its injection, it was possible to obviate the effects of removal of the pancreas in dogs, and to effect a restoration to health in cases of diabetes in man.

In order to prepare insulin, the fresh pancreas is finely minced and extracted with several changes of alcohol which, diluted by the water contained in the gland, is evaporated to a small bulk and poured into absolute alcohol. A white precipitate is produced which represents the crude insulin. The yield of insulin is increased by extracting in the first instance with alcohol containing sodium bicarbonate. Insulin forms an insoluble compound with picric acid, which is decomposed by weak hydrochloric acid with the formation of an hydrochloride. These properties are made use of to effect a further concentration of the active principle (Dudley's method).

The insulin so prepared is a white powder, easily soluble in water and in dilute alcohol, but insoluble in the ordinary fat solvents. It does not diffuse through parchment paper. It will withstand boiling for a short time and undergoes slow oxidation in alkaline solution. It gives some of the protein colour reactions, is destroyed by pepsin and trypsin, and is regarded by Dudley as probably being chemically allied to the peptides. Macleod has succeeded in extracting from the Langerhans islets of fish (where they occur apart from the glandular tissue) a preparation of insulin which did not give the biuret or Millon's reaction. Its chemical nature must therefore be regarded as undecided. 0.5 milligrammes injected into a normal rabbit causes a rapid diminution of the blood sugar, and finally the symptoms of hypoglycæmia already described. If insulin be injected into an animal from which the pancreas has been removed, the excretion both of sugar and of ketone bodies ceases, while the respiratory quotient rises, showing that the animal is utilising its sugar; and on the administration of carbohydrates glycogen is formed in the liver. The animal increases at the same time in weight and strength, and could apparently be maintained alive indefinitely. It is necessary, however, to inject a solution of insulin subcutaneously two or three times a day, since this substance is gradually used up or disappears from the body, and there is no pancreas present to manufacture it anew. Insulin is destroyed in the alimentary tract, so that it cannot be administered by the mouth with any effect.

One of the first questions which arose from the work on insulin was the fate of the blood sugar which so rapidly disappeared when insulin had been given. In attempting to answer this question we must first of all consider what are the sources of the tissue carbohydrate and blood sugar in both the normal and the diabetic individual. In the normal animal they may be regarded as derived either directly from ingested carbohydrate, or indirectly from the breakdown of protein, and probably to some extent also from fat. One thing seems certain, that, whether carbohydrate is ingested or not, its presence and continual metabolism in the tissues is essential to life. We have already seen that there is reason to suppose that when carbohydrate is not supplied to the body as such, there is production of carbohydrate in the body from fat, and we also have indisputable evidence of the conversion into carbohydrate of the deaminised residues from protein breakdown. The amount of carbohydrate at the disposal of the body at any time thus depends upon (1) the store present as glucose and glycogen in the blood and tissues;

(2) the amount accruing from absorption of carbohydrate; (3) the amount formed from protein and fat.

The excretion of sugar in diabetes is due to hyperglycæmia. This state of hyperglycæmia, and the excretion of sugar, persists even when the animal is completely starved or is fed on a pure protein or protein *plus* fat diet. Moreover, as in phloridzin glycosuria, we find a constant ratio between the sugar and the urinary nitrogen, the G : N ratio being usually about 2.8, and we conclude therefore that, in the absence of carbohydrate from the diet, the excess of sugar is derived from proteins. Glycogen disappears almost entirely from the liver.

The metabolism of the diabetic animal is characterised by partial failure of the liver and muscles to store carbohydrate, and further by the *accelerated endogenous production of carbohydrate* from protein, and probably also from fat. One of the most striking features of the condition is the rapid diminution of the fat depôts of the body, attended by a marked condition of lipæmia and accumulation of fat in the liver. The blood is so full of fat globules that it has been compared in appearance to strawberries and cream. One of the first effects of extirpation of the pancreas is therefore a rapid fat mobilisation, and the respiratory quotient agrees with that obtained when the metabolic needs of the body are being mainly satisfied at the expense of the fat. It has often been stated that the tissues also exhibit a diminished power to burn glucose. This is shown by the low respiratory quotient and by the fact that administration of glucose to the animal causes an almost corresponding increase in the amount of glucose excreted in the urine. But though this may be conceded, the power of oxidising sugar is certainly not abolished. With increased production and diminished storage of carbohydrate, the blood is flooded with sugar, which escapes by the kidneys, while the accelerated breakdown of protein and fat leads to the formation of ketone bodies in large amount.

In the diabetic subject, it seems quite clear that the effect of administering suitable amounts of insulin is to restore the carbohydrate metabolism to normal; in other words, to accelerate the combustion of carbohydrate and to allow the liver and muscles to carry a store of glycogen; hence, to lower the blood sugar; because the carbohydrate metabolism is restored, and because new formation of carbohydrate is reduced, ketone bodies speedily disappear from the blood, and therefore from the urine and breath. It is evident that, in the diabetic, insulin produces all these effects by supplementing the inadequate action of the pancreas.

In the normal animal or man, there is already an efficiently functioning pancreas, so that in administering insulin to them we are getting abnormal effects due to the presence of an excess of that substance. The effects of this excess of insulin are best understood if we consider them as an exaggeration of the effects of therapeutic doses on the diabetic, *i.e.* as displaying the same qualitative influences as in the normal metabolism of carbohydrate, but to an enhanced degree.

We should therefore expect the following effects to ensue when insulin is given in rather large doses to the normal animal; first, an increased storage of glycogen in the muscles and liver, together with an accelerated combustion of glucose in the tissues. Secondly, a reduction to a level far below the normal, of the formation of carbohydrate from protein and from fat. In consequence of both of these effects, there would be a large reduction in the blood-sugar level, with its attendant consequences. One of these consequences is the onset of convulsions; another is that the liver glycogen is now drawn upon, as will be explained later. How long the liver and muscles will be able to supply carbohydrate to the animal which is now deprived of the normal endogenous new formation of sugar, will depend on the total available store of carbohydrate in the

body at the time the dose of insulin was given, but it is certain that in fasting animals with rapid metabolism, such as mice, the store is very small. If the mouse were oxidising carbohydrate exclusively for its metabolism, however, its oxygen consumption shows that its store would last for only about twenty minutes if new formation from protein and fat ceased. If the action of insulin is that explained above, we should expect to find that, by stopping new formation and thus confining the animal's metabolism to its ready-formed carbohydrate, there would, if no more carbohydrate were supplied, be a rapid falling off in the respiratory exchange, accompanied by a fall of body temperature; while if the fall of body temperature were prevented by placing the animal in a thermostat, we should expect that the animal would die in about half an hour, or as soon as its carbohydrate was completely exhausted. This is what actually happens, and in other species of animals the fatal result depends on similar conditions, and is accompanied by a similar depletion of the body store of carbohydrate.

In the later stages, therefore, the glycogen content of the liver and muscles, instead of being raised, is greatly lowered.

The emptying of the liver glycogen in consequence of the fall of blood sugar is due to the effects of the lowered blood sugar on the central nervous system, from which efferent impulses pass to the liver *via* the sympathetic nerve supply.

We must now consider what happens to the glucose which disappears from the blood when insulin is given. It was suggested by Lesser that part of the glucose was oxidised, and, as happens in the oxidation of lactic acid in muscle during recovery, the remainder of the glucose was built up into glycogen, and researches by Best, Dale, Hoet and Marks have given good grounds for believing that the explanation lies along some such lines.

Best, Hoet and Marks showed that when the blood sugar of the eviscerated spinal cat was kept at a high level for two to five hours by intravenous injection of glucose, there was no demonstrable change in the glycogen content of the skeletal muscles. When insulin was also given, there was an accelerated rate of sugar disappearance, and an *increase* in the glycogen content of the muscles, irrespective of whether actual hypoglycæmia resulted or not, and this deposition of the glycogen was enough to account for from 40 to 50 per cent. of the sugar which had been lost from the blood. It may be concluded, then, that under the conditions of these experiments, much of the lost sugar was recoverable as glycogen.

Finally, Best, Dale, Hoet and Marks showed that the sugar which disappears from the body can be completely accounted for on the one hand by combustion and on the other hand by conversion into glycogen.

THE NORMAL FUNCTION OF INSULIN. Large amounts of carbohydrate can be dealt with by the normal individual without any appreciable loss of sugar by way of the urine; on the other hand, abstinence from carbohydrates for quite long periods does not lead to hypoglycæmia. This is no doubt due to the fact that protein, and to a less extent fat, can be converted into glucose, and thus supply the imperative needs of the body for carbohydrate. But all the experience of clinicians in the treatment of diabetes by insulin has shown that it is necessary to secure a proper balance between the amounts of insulin administered and carbohydrate ingested, as otherwise there will be either an excretion of glucose in the urine, or else the unpleasant effects of hypoglycæmia. In the normal functioning of the pancreas, since neither of these effects ensue, there must therefore be some means by which the amount of insulin liberated from the islet tissue corresponds with the amount of carbohydrate to be dealt with.

Apparently, when carbohydrate is taken by the mouth, as in the administration of glucose for the purposes of a test meal and blood-sugar curve, there is an accompanying liberation of insulin to deal with it; it is often seen that in a blood-sugar curve the blood sugar falls very rapidly after its initial rise, and reaches a level slightly below that of the blood in the fasting state.

The rapid fall is not because the absorption of the glucose from the alimentary canal is at an end; this is shown by the fact that in the diabetic subject the rapid fall is not seen, the high level persisting even for some hours after the ingestion of glucose which originated it. The fall in the normal subject

without doubt occurs because by that time the insulin production has been sufficient to reduce the blood sugar in spite of the continuing sugar absorption. For this reason it is found that if a second test meal of 50 grammes of glucose is given to a normal subject as soon as the blood sugar has reached its low level, there is little or no further rise in the blood sugar. It has even been shown that a transfusion into a diabetic subject of blood taken from a normal individual during the absorption of glucose, will lead to a fall in the blood sugar of the patient, just as though insulin had been given.

Macleod and collaborators and G. A. Clark have given some evidence that the liberation of insulin is controlled by influences reaching the pancreas by way of the vagus.

Just as the hyperglycæmia produced by adrenaline, or in any way, can be counteracted by insulin, so the hypoglycæmia brought about by an overdose of insulin can be relieved by administration of adrenaline if any glycogen is present in the liver.

Cannon, McIver and Bliss have shown that when insulin is given, there is excitation of the sympathetic system and a discharge of adrenaline from the suprarenals as soon as the blood sugar falls below about 0.07 per cent., which checks the further fall of blood sugar; conversely it is likely that the injection of adrenaline into the circulation leads to a setting free of insulin from the pancreas.

(5) DIABETES IN MAN. In its severer forms, the diabetes of man resembles very closely that produced in the dog by total extirpation of the pancreas. The output of urine is largely increased, and the urine, though light in colour, is of a high specific gravity, 1030 to 1035, and may contain from 5 to 10 per cent. of sugar. The appetite is largely increased, but the body wastes. The patient may die after some months or years in a condition of diabetic coma. Warning of the onset of this condition is given by the rise of ammonia in the urine and by the appearance of oxybutyric and aceto-acetic acids. The breath may smell of acetone, and this substance may also be present in the urine. On the other hand, the diabetic state is attended by diminished resistance of the tissues to infection. The patient may thus die of some such intercurrent infection before the onset of coma. In a few cases the pancreas is found to be atrophied or diseased, but in the large majority no marked pathological change is to be observed with the naked eye in this organ. Wherever it has been possible to apply refined methods of microscopical examination, some change has generally been found in the islets of Langerhans (Opie). We may find all grades between such cases and those in which there is still a considerable power of assimilation. In order to determine the grade of the disorder, it is usual to give a glucose test meal, and to examine the urine for sugar and make a blood-sugar curve. In many cases the sugar will disappear from the urine on the administration of a diet consisting entirely of proteins and fats. When this has been effected, carbohydrates may be added in small proportions to the diet up to the limit of the assimilatory powers of the patient. It seems that administration of any carbohydrate in excess of this limit is of disadvantage to the patient and hastens the progress of his disorder. When the power of assimilating carbohydrates is entirely abolished, the prognosis is absolutely fatal unless insulin be given. This point may be determined in two ways. In the first place, a patient with no power of carbohydrate assimilation will continue to excrete sugar in the urine on a pure protein-fat diet. Information may also be obtained from a study of his respiratory quotient. A very low respiratory quotient is a sign of the severity of the disorder.

As in the diabetes produced by extirpation of the pancreas, the patient may be restored to health, and kept in that condition, by the repeated administration of doses of insulin hypodermically. Care must be taken not to give

too large a dose, as the hypoglycæmia thereby produced is more immediately dangerous than the hyperglycæmia of the diabetic condition. This state of hypoglycæmia, if accidentally induced by an overdose, can be removed by administration of glucose, either orally or by subcutaneous injection. If the administration of insulin be intermitted, the patient returns at once to the diabetic condition.

The strength of insulin preparations must be carefully controlled for use by biological standardisation. The method is based on the reduction of the blood-sugar level of animals by the sample, as compared with that produced by an international standard preparation.

This study of the conditions of carbohydrate metabolism shows how all three classes of foodstuffs co-operate in the maintenance of the chemical processes which lie at the root of the existence and the activities of living organisms. Protoplasm, the actual living material, consists of a complex in which proteins, lipides, carbohydrates, nucleins, salts and water all play a part and of which each is an essential constituent. In the higher animals proteins are necessary to furnish the proteins of the tissues, and the food must contain just those amino-acids which are requisite for the building up of the proteins characteristic of each separate tissue. Moreover, certain groups of the protein molecule appear to be destined to serve as mother-substances of hormones and other chemical compounds which play a dynamic, rather than a static, part in the phenomena of life, and supply conditions of activity rather than material for the production of energy. The carbohydrates not only act as sources of energy, but are necessary to the building up of the proteins into the protoplasmic complex. Without them, moreover, this complex cannot properly utilise the fat contained in itself or supplied in its food. At the same time there is a certain possibility of inter-conversion between these different substances.

CHAPTER XXXI

THE BLOOD

IN the unicellular animals and in the lowest metazoa, the cells are bathed by the medium in which the organisms live, and are therefore exposed to all the changes which occur in the composition of this fluid. With the evolution of a body cavity filled with fluid, the tissue cells are bathed by an internal medium which is maintained practically constant in its characters for any given type. With increasing differentiation the fluid of the coelom, which may be called blood, becomes enclosed in branching systems of tubes, and its circulation is provided for by the development of contractile chambers at some point or points of the tubes. In all the higher animals, the blood circulates through a closed system of tubes, a constant flow being kept up by the action of the heart. It is separated from the tissue elements themselves by the walls of the blood vessels. The free interchange of material between blood and tissues is facilitated by the tenuity of the vascular wall. The interstices of the tissues contain a fluid, the 'tissue fluid,' which is formed by the transudation of materials from the blood through the walls of the capillaries, and the interchange between the blood and the tissue cells is effected through this fluid. In a similar manner, excess of water and certain dissolved constituents of the tissue fluid freely pass into special channels, known as the lymphatics, and by these are returned again to the blood. Since the function of the blood is to act as the common nutritive medium of all parts of the body, it has to convey food materials and oxygen to the tissues. From these it receives in exchange their waste products, namely, carbon dioxide and the results of nitrogenous metabolism, and carries them away to the excretory organs, such as the lungs and kidneys, by which they are eliminated. It is evident that the composition of the blood must vary from time to time and place to place according to the condition of activity and the function of the organ which it is traversing. The organs of the body are adjusted to respond to very minute changes in the composition of the circulating fluid, and add to or subtract from its constituents according as these are present in deficiency or excess. The changes are therefore kept within infinitesimal limits and we may therefore treat the blood as a fluid of approximately constant composition and qualities.

Blood obtained from a mammal is an opaque fluid varying in tint according to the vessel from which it is derived, being scarlet when taken from an artery, purplish in colour when taken from a vein, the difference being determined by the degree of oxygenation of the blood. On shaking venous blood with air, it takes up oxygen and acquires the scarlet colour characteristic of arterial blood. If examined in a thin layer under the microscope, its opacity is seen to be due to the fact that it is not homogeneous, but consists of a number of *corpuscles* of different kinds, suspended in about their own bulk of a light yellow transparent fluid, the *plasma*. In order to make out the characters of these corpuscles the blood should be diluted with some 'normal' fluid, such as 0.9 per cent. sodium chloride. It is then seen to

contain three main classes of corpuscles. Much the most numerous and conspicuous are the *red corpuscles*. Next most conspicuous are the *white corpuscles*; the third type of formed elements are very small and are called the *blood platelets*. The average numbers of these formed elements per cubic millimetre of normal human blood are as follows:

Red corpuscles	5,400,000 (some say 6,000,000)
White corpuscles	10,000
Platelets	300,000 (variable).

In the whole body there are about 25 billion red corpuscles and about 50,000 million white corpuscles.

Unless special precautions are taken, the examination of blood obtained from a blood vessel is interfered with by the process of clotting, which ensues shortly after the blood has left the vessels. If blood be received into a beaker it is at first perfectly fluid. After a space of time, varying from three to eight minutes, it begins to be viscous, and if poured out of the beaker leaves an adherent layer on the sides of the vessel. A minute later the whole mass of the blood becomes solid and the beaker can be inverted without spilling its contents. If a section be made of this blood clot, it is found to

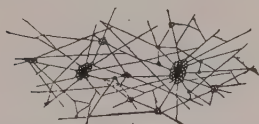


FIG. 328. Network of Fibrin, after washing away the corpuscles from a film of blood that has been allowed to clot; many of the filaments radiate from little clumps of blood platelets. (SCHAFER.)

owe its solidity to a network of fine threads of a protein substance named *fibrin*, which have formed throughout the plasma and enclosed the corpuscles in their meshes (Fig. 328). On leaving the clot for some hours, drops of yellow fluid appear on its surface and run together. The whole clot contracts, and finally there is a reduced clot, floating or suspended in a yellowish fluid known as *serum*. If after the blood has left the vessels it be whipped with a bunch of twigs, or stirred with a glass rod,

the filaments of fibrin as they are formed are deposited on the twigs. After three or four minutes the twigs can be withdrawn and the spongy fibrin collected. The blood which is left consists only of the corpuscles *plus serum*, and it will not clot since its fibrin has been removed. It is known as *defibrinated blood*. Since the corpuscles are apparently unchanged in the meshes of the clot, and clotting can be produced in blood plasma entirely separated from corpuscles, we must look upon the process of coagulation as determined in the main by changes in the blood plasma. We can regard the blood therefore as a tissue consisting of a fluid matrix, which is extremely unstable and undergoes change when it leaves the vessels, and as having floating in its matrix formed elements or cells of various kinds.

THE WHITE BLOOD CORPUSCLES

These are of various kinds, some of which, when kept warm, exhibit amoeboid movements. Amoeboid cells are a constant constituent of the coelomic fluid in all classes of animals. Even in the lower metazoa, where there is not yet a body cavity, wandering mesoderm cells are present which apparently discharge functions analogous in all respects to those of the white blood corpuscles of mammals.

The differentiation of the various types of corpuscles is more easily made if recourse be had to staining with mixtures of aniline dyes. This method was introduced by Ehrlich, who showed that some of them contained granules which were stained by acid dyes such as eosin, and these corpuscles

he called *eosinophile*. Others, the *basophile* cells, were stainable with basic dyes, while a third type were only lightly stainable, and were called *neutrophile* leucocytes. It is now customary to classify the white corpuscles as shown below, the figures expressing the average results of what is called a *differential cell count*. This shows, out of a total of 100 white cells, how many of each variety are present.

(1) GRANULOCYTES.

(a) Neutrophile. Approximate average, 68 to 70 per cent.

(b) Eosinophile. Average, 3 per cent.

(c) Basophile (mast cells). Average, 0.5 per cent.

(2) MONOCYTES.

(a) Large mononuclears. } Average, 4
(b) Transitional. } per cent.

(3) LYMPHOCYTES. Average, 23 to 25 per cent.

An acid dye is generally a salt in which the colouring matter plays the part of an acid radical. Thus eosin is the sodium salt of the coloured acid tetrabrom-fluorescein. Basic dyes possess basic colour radicals. Methylene blue, an example of this class, is the chloride of the coloured base tetramethyldiphenthiazine. Neutral dyes, according to Ehrlich, are those in which a colour base is combined with a colour acid, such as the eosinate of methylene blue, or the picrate of rosaniline.

The various white cells have the following characters :

(1) GRANULOCYTES.—(a) *The Neutrophile Cells*, or *polymorphonuclear* leucocytes. These present a lobed nucleus, and their protoplasm contains abundant fine neutrophile granules which stain with Ehrlich's triacid and with the May-Giemsa stains. The cytoplasm contains proteolytic enzymes capable of causing autolysis (hence the liquefaction of pus on standing). These cells are actively amœboid and phagocytic, and their numbers rapidly increase in pyogenic infections.

(b) *The Eosinophile Cells*. The nucleus is generally single, but is often crescent-shaped or reniform. The protoplasm is crammed with large, discrete, highly refractive granules, which stain deeply with eosin and give micro-chemical reactions for iron as well as phosphorus. The eosinophile cells are not normally phagocytic.

(c) *The Basophile (or Mast) Cells*. These, which are somewhat smaller than the polymorphonuclear cells, have a lobed or tri-lobed nucleus and present a number of granules in their protoplasm which stain deeply with basic dyes. In normal blood the basophile cells are rare, though they appear, sometimes in large numbers, in disease, and are normally present in the blood of some of the lower animals.

(2) MONOCYTES—(Histiocytes).—These are large vacuolated cells with a single nucleus, and with fairly abundant faintly granular cytoplasm. The monocytes are rare cells in normal blood, but they are of considerable importance. They have the property of ingesting foreign particles of almost any sort, and for this reason are able to take up certain intra-vitam dyes, such as pyrrol or trypan blue, or granules of Indian ink or carmine.

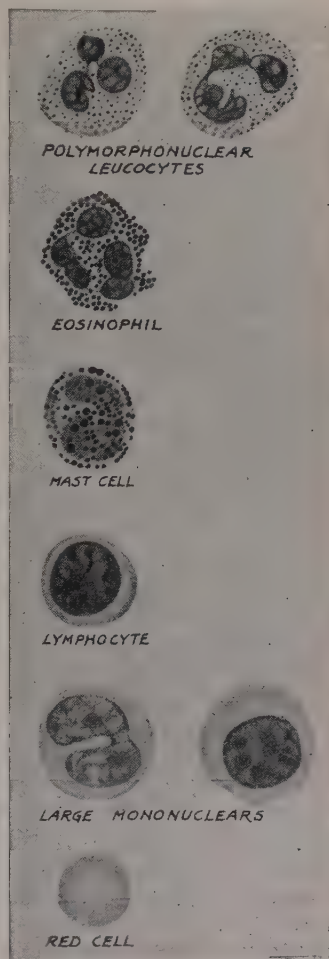


FIG. 329. Various forms of Blood Corpuscles.

The *transitional cells* are more numerous, as a rule, than the monocytes, forming about 4 per cent. of the total whites. Their general structure resembles that of the monocytes, but they are smaller. Their nucleus is indented or slightly lobed, and the cytoplasm has fine granules which stain with azur.

(3) **LYMPHOCYTES.**—These abundant cells, smaller than the other mononucleated white cells, and of more uniform diameter (about 8 μ), have a round nucleus and only a small amount of cytoplasm, which has very few granules, but such as it has are coarse and stain by azur.

The leucocytes as a whole undergo variations in number according to the physiological state of the animal, and are increased during digestion, especially of a protein meal.

FORMATION OF THE LEUCOCYTES. In classifying the white corpuscles of the blood, it is essential to know whether the different varieties we have described represent phases in one and the same corpuscle or a number of different cells of separate origin. The question as to the origin of each kind of leucocyte cannot be regarded as settled. According to some observers, Maximow and others, all the cells, red and white, are derived from one kind of cell called a *hæmocytoblast*. Others regard each type as originating from one of two or more distinct kinds of cells. Since division of the leucocytes in the blood itself appears to be an occurrence of the utmost rarity, we must locate the original seat of formation of these cells in two tissues.

Lymphocytes are derived from the adenoid tissue forming the lymphatic glands and the lymph nodules surrounding so many of the mucous cavities. These lymphatic nodules present towards their centre a clearer zone, consisting of cells rather larger than those of the periphery and known as the 'germ centre.' The nuclei in these cells present a well-marked reticular arrangement, and mitotic figures are often to be seen. By the division of these cells lymphocytes are formed, pushing towards the periphery of the nodule, where they make their way into the lymph sinus and are carried slowly by the lymph into the blood.

The other tissue mainly concerned in the formation of leucocytes is the bone marrow. This is the chief blood-forming tissue of the body, since it is responsible also for the production of all red blood corpuscles which are formed during adult life. In the red marrow are seen a number of cells known as *myelocytes*. These contain a single rounded nucleus and a well-marked protoplasm which may be non-granular or may contain granules, generally eosinophile in character but sometimes basophile. It is stated that all intermediate stages are to be found in the bone marrow between these myelocytes and the polymorphonuclear leucocyte as well as the eosinophile leucocyte. It is certain that in the disease leukæmia, which is associated with an increased number of leucocytes in the blood, there may be an increase either of eosinophile cells or of neutrophile cells, and either condition is associated with changes in the red bone marrow. We may therefore provisionally arrange the leucocytes of the blood according to their origin as follows:

- (1) Small lymphocyte derived from lymphoid tissue.
- (2) Large mononuclear or histiocyte. These are derived from the fixed histiocytes of the tissues and other varieties of reticulo-endothelial cells.
- (3) Polymorphonuclear leucocyte formed in bone marrow.
- (4) Eosinophile cell derived from similar cells in the bone marrow.

FUNCTIONS OF THE LEUCOCYTES. The polymorphonuclear leucocytes present two phenomena, that of amœboid movement and that of ingesting foreign particles which may be presented to them. On account of

this power of eating up foreign particles they are frequently spoken of as 'phagocytes,' in this respect resembling unicellular organisms and the undifferentiated cells of many kinds of tissue. All the phenomena connected with the process of *inflammation* in higher animals are directed to the assemblage of polymorphonuclear leucocytes at the spot which is the seat of injury or of infection, so that they may devour and remove either the injured tissue or the invading micro-organisms. This process therefore plays an important part in determining the immunity of any animal against infection; though in the higher animals it is assisted by a number of other mechanisms directed towards the same end.

THE RETICULO-ENDOTHELIAL SYSTEM.—In addition to the polymorphonuclear leucocytes, certain other cells have phagocytic properties. These are the monocytes of the blood, and certain widely dispersed tissue cells. All of these arise, like the blood cells, from the mesenchyme of the embryo. Of the mesenchyme cells, some become the *fibroblasts* of the connective tissues. A number, however, retain their embryonic developmental potentialities, and become converted into tissue histiocytes belonging to one of two types, called respectively the *free and fixed histiocytes*. The *free histiocytes*, wandering cells, or macrophages, have phagocytic properties, and are to be found in the connective tissues. By a change in their granulation they may become the *mast cells*, familiar as inhabitants of the connective tissues. The *fixed histiocytes*, or 'resting wandering' cells, are to be found in large numbers in the serous membranes, especially in the omentum, and also as histiocytes which have taken up the position of an endothelial lining. This scattered system of specialised 'endothelial' cells is sometimes called the *reticulo-endothelial system*. Examples are the so-called 'endothelial cells' which form the incomplete lining of the sinusoids of the liver and spleen. In the *liver* the cells are known as the *Kupffer* or stellate cells. This widely disseminated system of cells comprises cells of very differing function, shape and appearance, but they all possess in common the property of ingesting foreign particles of varying grades of size. Even relatively coarsely particulate matter is taken up by these cells, *e.g.* by the Kupffer cells of the liver. Thus, if Indian ink or carmine is injected intravenously, granules of the pigment are to be found shortly afterwards in the Kupffer cells, and in the similar cells of the spleen and marrow, as well as in the polymorphonuclear leucocytes and monocytes of the blood stream. Certain colloidal dyes, *e.g.* pyrrol blue, are also taken up by the cells.

Phagocytosis is not merely of use in protecting the tissues from infection. Whenever any surplus or dead tissue has to be cleared away, whether as the result of injury or in the course of the metamorphosis of organs, the phagocytic cells of the tissues play an important part. Thus the absorption of the tail of the tadpole is effected in the same way by means of phagocytes. In mammals, including man, the moulding of the long bones which occurs in the process of growth is effected by continual and coincident processes of absorption and new formation of bone. The absorption is carried out by means of special phagocytes called osteoclasts.

The other functions, which have been ascribed to leucocytes, are unimportant as compared with their rôle as phagocytes, and are all of them questionable. Thus some authors ascribe to leucocytes a significant part in the taking up of fat from the intestine and its carriage into the lymphatic system. In the coagulation of the blood, the leucocytes have been supposed to act by the discharge of substances which may be precursors of thrombin. The leucocytes and lymphocytes are also believed to play a part in the formation of anti-toxins.

THE RED BLOOD CORPUSCLES

The red blood corpuscles, or *erythrocytes*, in man are non-nucleated biconcave discs, which when in the body are about $8.8\ \mu$ in diameter and about one-third of this in thickness. In the dried, fixed film they are, owing to

shrinkage, only about 7 to 8 μ in diameter. The colour of a single corpuscle when viewed under the microscope is yellow, the red colour being apparent only when larger numbers are seen together. The red corpuscles form about 50 per cent. of the total mass of the blood. They are soft, flexible and elastic, so that they can readily squeeze through apertures and canals narrower than themselves, without undergoing permanent distortion. Each red corpuscle has been described as consisting of a framework or stroma, composed chiefly of protein material, containing in its meshes a red colouring matter, hæmoglobin, to which is due the colour of the corpuscles and of the blood itself. An alternative view is that the corpuscle consists of a strong solution of hæmoglobin contained within an envelope, partly fatty in nature, and consisting of a combination of proteins and lipides.

In nearly all mammalia the red corpuscles are of the character described. In the camel they are oval in shape, but otherwise resemble the corpuscles of other mammals. In all other classes of vertebrata the red corpuscles are oval, nucleated cells. The hæmoglobin is diffused through the protoplasm of the cell body and does not extend to the nucleus. During the early part of foetal life the corpuscles of mammals are also nucleated, but



FIG. 330. Human Red Corpuscles.
On the right of the figure the corpuscles are seen on edge. (SWALE VINCENT.)

in the adult condition the erythrocytes, except under abnormal conditions, lose all traces of the nucleus before entering the blood stream. The small size, and great number, of the red corpuscles determine that a very large area of surface of red corpuscles is exposed to the plasma. The volume of each corpuscle has been estimated as $\cdot 0000000722$ mm.³, and its surface as $\cdot 000128$ mm.², so that the total surface of red corpuscles in the blood of a man weighing about 70 kilos. (assuming his total blood as $\frac{1}{13}$ of the

body weight) would be about 3000 sq. metres, or 1500 times the surface of the body itself. This great extent of surface is of importance in facilitating the exchange of material, especially oxygen, between the corpuscle and the surrounding plasma.

Bürker has shown that in various species there is a close relation between the surface area of the red cell and its hæmoglobin content, the ratio being constant at about 32×10^{-14} grammes of hæmoglobin per square μ of corpuscle surface.

OSMOTIC RELATIONSHIPS OF THE RED CORPUSCLE. If the blood plasma be concentrated by evaporation or by the addition of neutral salts, its osmotic pressure rises, and water diffuses from the corpuscles into the plasma in order to equalise the osmotic pressure within and without the corpuscle. The latter therefore becomes wrinkled or *crenated*. On the other hand, dilution of the plasma diminishes its osmotic pressure below that of the corpuscles, and water therefore passes into the latter, which swell up and become spherical; and, if the plasma be made sufficiently dilute, the corpuscles burst and liberate the hæmoglobin they contain. This is called *hæmolysis*. The corpuscles of mammalian blood neither gain nor lose volume in a solution containing 0.9 per cent. sodium chloride. The osmotic pressure as determined by the freezing-point of such a solution is identical with that of the blood, which in most mammals has a freezing point between -0.54° and -0.60° C. The salt solution which is normal for frogs' blood contains only 0.65 per cent. sodium chloride.

The behaviour of the red corpuscle, when immersed in various solutions, shows that its most external layer is impermeable to most neutral salts as well as to cane sugar and glucose. We may therefore make isotonic solutions with sodium chloride, sodium sulphate, potassium nitrate, or cane sugar. On the other hand, a solution of urea behaves towards the corpuscles like distilled water. If some red corpuscles be added to a 1 per cent. solution of urea in normal salt solution, they neither shrink nor swell; and if a 1 or 5 per cent. solution of urea in water be added to defibrinated blood, the corpuscles will swell up and burst just as if distilled water had been added. There are many substances to which the corpuscles are permeable, *e.g.* alcohol, chloroform, ether, &c. In their permeability the corpuscles resemble most other vegetable and animal cells in permitting the passage of those substances that are soluble in lipides, which are invariable constituents of all living cells. According to Overton the external limiting pellicle of the red corpuscles, as in most living cells, is formed by a lecithin-cholesterol compound, whose solvent power determines the permeability of the cell by foreign substances. The red corpuscles are not of rigidly fixed size when in the body. The circumstance which is chiefly responsible for change of size in the body is alteration in the reaction of the blood plasma; reduction of the alkalinity of the plasma causes swelling of the corpuscles, and *vice versa*. Hence it follows that the corpuscular volume is slightly greater in venous than in arterial blood.

CHEMISTRY OF THE RED BLOOD CORPUSCLES

The red corpuscle consists of hæmoglobin and stroma. By various means it is possible to destroy this association and to dissolve out the hæmoglobin, leaving the colourless swollen-up stromata floating in the plasma. At the same time the blood becomes darker but more transparent, and is spoken of as 'laked' or hæmolysed blood.

It has been thought by Schwann, Schafer and others that the red corpuscle consists of a solution of hæmoglobin included within an envelope which contains lecithin and cholesterol and forms the stroma. The blood corpuscles contain a greater percentage of solids than any soft tissue of the body. The blood corpuscles have 37 per cent. solids, as against muscular tissue with 25 per cent. or nervous with 22 per cent. solids. Of these solids, 95 per cent. consist of hæmoglobin, so that the solution would have to contain at least 30 per cent. hæmoglobin, which is far beyond its solubility. Some form of combination is therefore necessary in the corpuscles, if merely to keep the hæmoglobin from separating out in a crystalline form.

Blood may be laked by any of the following means:

- (a) Addition of a small amount of ether or other lipide solvents.
- (b) Free dilution with water, or dialysis.
- (c) Alternate freezing and thawing of the blood.
- (d) Addition of bile salts or of saponin.
- (e) The action of foreign blood serum or of various hæmolysins whose nature we shall discuss later.

From such laked blood we may prepare either hæmoglobin or stroma.

In investigations on the chemistry of the red cells it is usual first to remove the plasma by centrifugalisation and washing. The blood, which has been defibrinated, or prevented from clotting by the addition of a little sodium oxalate, is centrifuged until all the formed elements are thrown down as a solid cake at the bottom of the tube. The tube is then filled up with normal saline fluid and again centrifuged, and this process repeated twice in order to wash away adherent plasma or serum. After the final washing the paste of corpuscles can be laked; for this, two volumes of distilled water saturated with ether are added to one volume of caked corpuscles. The fluid is once more centrifuged in order to throw down white blood corpuscles. A 1 per cent. solution of acid sodium sulphate is now added drop by drop until the solution acquires the opaque

appearance presented by ordinary blood. On centrifuging, the stromata are thrown down, and can be collected and washed with distilled water several times on the centrifuge.

Removal of stromata from laked cell solutions can be effected also by shaking for an hour or two with asbestos pulp and then removing this, with adherent stromata, by centrifugalisation.

The stroma protein forms only about 4 per cent. of the total solids of the corpuscle. It is insoluble in dilute acids, but easily soluble in dilute alkalis. On gastric digestion the greater part dissolves, leaving a residue which is rich in phosphorus, and resembles nuclein. The residue also contains a large quantity of lecithin. According to Wright the nuclein residue yields purine bases on hydrolysis, and is therefore rightly classed with the other nucleins from tissue cells and contained in nuclei.

From a laked solution of corpuscles, oxyhæmoglobin can be obtained in a crystalline form with varying readiness according to the animal from which the blood is derived. Thus in the case of the rat, the guinea-pig, the dog and the horse, it is sufficient merely to cool the laked blood, preferably in a freezing mixture to about -10°C ., in order to obtain a large crop of hæmoglobin crystals. Crystallisation is facilitated by the addition of 25 per cent. of absolute alcohol to the mixture, but the use of alcohol tends to interfere with the subsequent purification and solubility of the hæmoglobin.

To avoid this, the following simple method depends on the fact that oxyhæmoglobin is less soluble than reduced hæmoglobin. Washed horse corpuscles are dialysed in collodion sacs against the osmotic pressure of the hæmoglobin. When fully laked, *débris* is removed by centrifugalisation, and then the cooled solution well oxygenated, when oxyhæmoglobin crystals separate out. These can be collected, suspended in distilled water, and reduced *in vacuo*, when they dissolve; on re-oxygenation the solution again crystallises.

Heidelberger laves by water and toluene, and passes a mixture of four parts CO_2 to one part oxygen; this yields crystals of the free acid of hæmoglobin, which can be dissolved in dilute sodium carbonate and recrystallised by again passing CO_2 and oxygen; finally the salts are removed by dialysis.

PROPERTIES OF HÆMOGLOBIN. The crystals thus obtained are as a rule microscopic in size. Most animals yield an oxyhæmoglobin which crystallises in rhombic prisms or needles belonging to the rhombic system. In the guinea-pig the crystals are tetrahedral in form, while the oxyhæmoglobin of the squirrel crystallises normally in the form of six-sided plates. On recrystallisation however, a squirrel's hæmoglobin can be obtained as a mixture of rhombic prisms with rhombic tetrahedra. The solubility of the crystals differs according to the animal from which they have been derived, and is in direct proportion to the difficulty with which the crystals are obtained. They are more soluble in alkalis than in water. The elementary analysis of oxyhæmoglobin crystals shows that it contains carbon, hydrogen, nitrogen, oxygen, sulphur and iron.

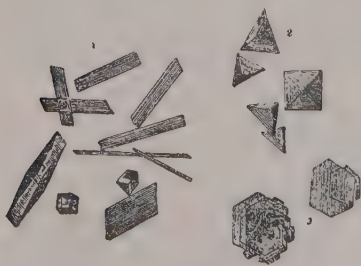


FIG. 331. Crystals of Oxyhæmoglobin.
1. From rat. 2. From guinea-pig.
3. From squirrel.

The chief differences between various animals appear to have relation to the sulphur. All specimens are alike in containing a constant proportion of iron, viz. 0.336 per cent.

Hæmoglobin readily combines with free oxygen to form oxyhæmoglobin, and it is found that for each atom of iron two atoms of oxygen can be taken up, *i.e.* 400 c.c. of oxygen per gramme of iron present as hæmoglobin. This corresponds to an oxygen capacity of about 1.32 c.c. oxygen per gramme of hæmoglobin, if we take 17,000 as the molecular weight for one atom of iron. Oxyhæmoglobin is thus a compound, in definite proportions, of oxygen and hæmoglobin or 'reduced hæmoglobin.' It can be easily dissociated and is split up by such simple means as exposure to a vacuum (*v.* Chapter XXXIX.);

the fluid gives off oxygen and the colour changes from a brilliant scarlet to a dull bluish red. The same change can be effected by treating a solution of oxyhæmoglobin with reducing agents such as hydrazine, sodium hydro-sulphite ($\text{Na}_2\text{S}_2\text{O}_4$) or ammonium sulphide; in the latter case reduction is aided by gently warming the solution. The oxygen in oxyhæmoglobin can be replaced by equivalent quantities of other gases. Thus if carbon monoxide gas be led through a solution of oxyhæmoglobin, oxygen is given off, and its place is taken by an equal volume of carbon monoxide with the formation of a more stable compound, carbon monoxide hæmoglobin. This body is dissociated only with extreme slowness and is unaffected by the addition of reducing agents. By using special precautions to prevent oxidation of the gas, the carbon monoxide can be replaced in this compound by nitric oxide,

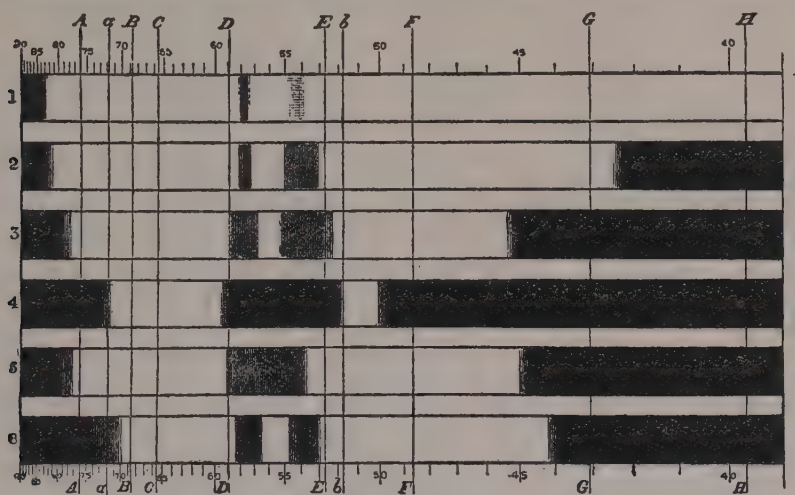


FIG. 332. The Spectra of Oxyhæmoglobin in different Grades of Concentration, of (reduced) Hæmoglobin, and of Carbon Monoxide Hæmoglobin. (After PREYER and GAMGEE.)

1 to 4. Solution of oxyhæmoglobin containing (1) less than 0.01 per cent., (2) 0.09 per cent., (3) 0.37 per cent., (4) 0.8 per cent. (5) Solution of reduced hæmoglobin containing about 0.2 per cent. (6) Solution of carbon monoxide hæmoglobin. In each of the six cases the layer brought before the spectroscope was 1 cm. in thickness. The letters (A, α, etc.) indicate Fraunhofer's lines and the figures wavelengths expressed in $\frac{1}{100,000}$ millimetre.

NO. We have therefore a series of three compounds which can be arranged in order of stability thus :

NO-hæmoglobin.
CO-hæmoglobin.
O₂-hæmoglobin.

The poisonous properties of carbon monoxide are chiefly due to its power of turning out the oxygen from the oxyhæmoglobin, thus depriving the tissues of the oxygen which is normally carried to them by the red corpuscles.

Hæmoglobin and its derivatives give well-marked absorption spectra. Thus dilute solutions of oxyhæmoglobin show two well-marked absorption bands between Fraunhofer's lines D and E. The centre of the band nearest to D corresponds to λ 579, and is often spoken of as the band α , while the second band, the one next to E, which can be called the band β , is broader, has less sharply defined edges, and its centre corresponds approximately to λ 544. On concentrating the solution or using thicker layers, a point is reached at which the two bands fuse into one, and with a still stronger solu-

tion the whole of the spectrum is absorbed with the exception of the red end.

If a reducing agent be added to the solution of oxyhæmoglobin, the two bands disappear and their place is taken by a more diffuse band lying midway between the two (Fig. 332, 5), its centre corresponding to λ 555. This is the absorption spectrum of hæmoglobin or reduced hæmoglobin.

The spectrum of carboxyhæmoglobin is very similar to that of oxyhæmoglobin, the *a* band being slightly (about 50 A.U.) nearer to the violet end. In a mixture of oxy- and carboxy-hæmoglobin, the shift of the *a* band is proportional to the fraction of the hæmoglobin present as the carboxy-compound, a fact which has been utilised by Hartridge for the determination of carboxy-hæmoglobin by means of his reversion-spectroscope. It is of a brighter red than oxyhæmoglobin, and on diluting the blood to a large extent, oxyhæmoglobin acquires a yellowish tint, while the pink colour of CO-hæmoglobin is retained. The fact that CO-hæmoglobin is not altered by reducing agents can be shown by adding ammonium sulphide to CO-hæmoglobin and examining with the spectroscope, when no change is observed.

All these derivatives of hæmoglobin, besides their absorption bands in the visible spectrum, have characteristic absorption of light in the ultra-violet spectrum. In the case of oxyhæmoglobin this absorption causes a band (Soret's band) which occupies the greater part of the spectral region between Fraunhofer's lines G and H. In reduced hæmoglobin this band is displaced towards the visible part of the spectrum.

Another compound of hæmoglobin with oxygen is *methæmoglobin*. This substance is not of normal occurrence in the body. It may be prepared by the addition of a ferricyanide, permanganate, or nitrite, or other oxidising agents to alkaline laked blood, or to solutions of oxyhæmoglobin. It is a chocolate-brown substance, crystallisable, and gives a distinct absorption band in the red between Fraunhofer's lines C and D. It is unaltered by exposure to a vacuum. On treatment with reducing agents, however, such as hydrosulphite, the methæmoglobin is converted into hæmoglobin, from which, by shaking with air, oxyhæmoglobin can be reformed. The fact that methæmoglobin cannot be reduced by exposure to a vacuum indicates that it is a compound of oxygen with hæmoglobin, in which the oxygen is in a different state of combination. According to Buckmaster methæmoglobin contains only half as much oxygen as oxyhæmoglobin. Conant and Scott believe it to contain only one quarter as much, and that the iron is in the ferrous state in hæmoglobin, but in the ferric state in methæmoglobin. The change from oxyhæmoglobin to methæmoglobin is not effected, however, by a simple shifting of the oxygen groups, but must be assumed to involve two distinct events. The whole of the oxygen in loose combination with hæmoglobin is given off, and oxygen from the reagents is added in its place. When ferricyanide is used the reaction would be :—



Since the whole of the oxygen in the oxyhæmoglobin is given off on the addition of potassium ferricyanide, we may use this fact in order to determine the total amount of oxygen in combination in the blood.

DERIVATIVES OF HÆMOGLOBIN. Hæmoglobin is a compound of an iron-containing coloured group (the prosthetic group) with a protein which varies somewhat in different animals. The prosthetic group is identical in every case where it has been examined. A separation of the prosthetic group from the protein moiety can be effected with extreme ease, and occurs whenever the hæmoglobin is treated with weak acids, with alkalies, or is heated above 70° C. The protein group is known as *globin*.

It is a strongly basic protein, classified with the histones, since it yields a considerable proportion of diamino-acids on hydrolysis. Unless prepared with great care the globin from blood is obtained in a denatured condition. Undenatured globin is prepared by R. Hill and Holden by breaking up oxyhæmoglobin solution with the smallest possible amount of dilute HCl at -2°C ., adding cold water, ether and kieselguhr and shaking well. It is then filtered and kept at -2° overnight. Meta-protein is thrown down by adding ammonia, and is filtered off. The filtrate is freed from ether by vacuum treatment and the salts removed by dialysis.

Hæmoglobin yields about 94 per cent. of globin and about 4.5 per cent. of the chromogenic group, hæmatin. In order to obtain hæmatin in a pure condition, it is usual to start with the crystalline derivative of hæmoglobin known as *hæmin*. When some dried blood is heated with a crystal of common salt and glacial acetic acid on a slide, a residue is obtained in which a number of reddish-brown needles are embedded, known as Teichmann's crystals or hæmin crystals (Fig. 333). The preparation of these crystals is often used as a convenient test for the identification of blood.

In order to obtain them in large quantities the following method, devised by Chalfejev, is employed. One volume of defibrinated blood is added to four volumes of glacial acetic acid previously heated to 80°C . As soon as the temperature has fallen to 60°C . the liquid is again warmed, and then allowed to cool. Crystals are formed which are allowed to stand for twelve hours and are then separated and washed by decantation, first with distilled water and then with graduated strengths of alcohol. In order to purify these crystals, the crude material is shaken for fifteen minutes with a mixture of chloroform and pyridine. The solution is filtered and then thrown into glacial acetic acid previously saturated with sodium chloride and heated to 105°C . A few drops of concentrated hydrochloric acid are then added and the mixture allowed to stand for twenty-four hours. The crystals which separate out are filtered off, washed with dilute acetic acid, and then dried.

Hæmin crystals have been regarded as hydrochloride of hæmatin. Elementary analysis shows that they have the following formula (Fischer): $\text{C}_{34}\text{H}_{30}\text{O}_4\text{N}_4\text{ClFe}$. By dissolving hæmin in alkalis and throwing the solution into an excess of acid, a precipitate is obtained which is hæmatin. Hæmatin forms a powder of bluish-black colour and metallic lustre. It is insoluble in water, alcohol or ether, but is slightly soluble in glacial acetic acid and in absolute alcohol. It is easily soluble in concentrated sulphuric acid, but undergoes decomposition, losing its atom of iron and being transformed into *hæmatoporphyrin*, which forms a deep purple solution. The formula of hæmatin is probably $\text{C}_{34}\text{H}_{30}\text{O}_4\text{N}_4\text{Fe.OH}$. Its compounds with acids and alkalis are spoken of as acid and alkaline hæmatin, and each gives a characteristic absorption spectrum (Fig. 334). The alkaline solutions exhibit one indistinct absorption band between C and D, the acid solutions an absorption band also between C and D but nearer to C, and resembling somewhat the band presented by methæmoglobin.

Hæmochromogen. According to Hoppe-Seyler and Gamgee, pure solutions of hæmatin in alkalis are quite unaffected by reducing agents; in the presence of certain foreign matters however, alkaline hæmatin, when treated with reducing agents, exhibits a spectrum known as hæmochromogen. The same change is further observed when alkaline hæmatin, made by the action of alkalis on ordinary blood, is treated with reducing agents such as ammonium sulphide. These facts receive an explanation from the discovery



FIG. 333. Hæmin Crystals

of Anson and Mirsky that hæmochromogen is a compound of reduced hæmatin with a nitrogenous compound. When made from blood, the nitrogenous compound is a denatured globin, but other proteins, or nicotine, hydrazine, pyridine or ammonia can take its place, to yield almost identical hæmochromogens. When hæmochromogen is prepared from blood, the changes would be :

Oxyhæmoglobin + alkali $\rightarrow$ Hæmatin + Globin (denatured)

Hæmatin + globin (den.) [+ reducing agent] $\rightarrow$ hæmochromogen.

When prepared from other compounds, *e.g.* pyridine, the hæmochromogen

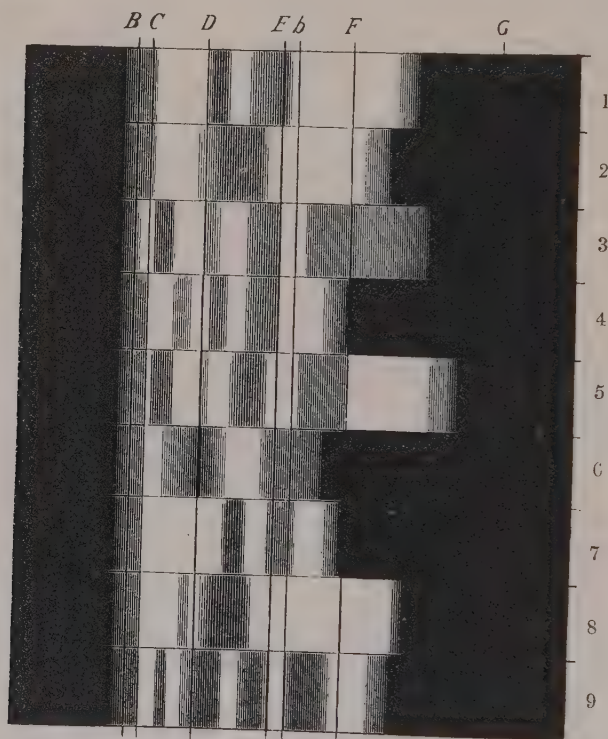


FIG. 334. Absorption Spectra of Hæmoglobin and its Derivatives. (From MACMUNN.)

- | | |
|----------------------------|--|
| 1. Oxyhæmoglobin. | 6. Alkaline hæmatin in rectified spirit. |
| 2. Reduced hæmoglobin. | 7. Hæmochromogen. |
| 3. Methæmoglobin. | 8. Acid hæmatoporphyrin. |
| 4. Alkaline methæmoglobin. | 9. Alkaline hæmatoporphyrin. |
| 5. Acid hæmatin in ether. | |

similarly consists of a compound of reduced hæmatin and pyridine. When reduced hæmoglobin is treated with alkali, the globin is denatured, but not split off, and hæmochromogen results at once. It is evident then that hæmochromogen differs from hæmoglobin essentially in the fact that its protein is denatured, and in existing only in the reduced form; when oxidised it yields alkaline hæmatin and the protein or other nitrogenous body is split off.

The hæmochromogens in solution have a cherry-red colour, and when sufficiently diluted show two well-marked absorption bands (Fig. 334, 7). Of the two absorption bands which are situated between D and E, that nearest to D has very sharply defined borders; the position of the two absorption bands may be given in terms of their wavelengths as follows: λ 555 to 559

and λ 525 to 528. The band nearest D is given by hæmochromogen solutions diluted until there is only one part of the pigment in 25,000 parts of water, so that it is an even more delicate test for blood than is the spectrum of oxy-hæmoglobin itself. When CO-hæmoglobin is treated in the same way with alkali in the absence of oxygen, a body CO-hæmochromogen is formed which contains exactly the same volume of CO in combination as the original CO-hæmoglobin. This fact, combined with the possibility of reducing ordinary alkaline hæmatin, indicates that the group of atoms which in hæmoglobin is responsible for taking up oxygen or carbon monoxide gas passes unchanged into the hæmochromogen molecule.

Cytochrome. A substance closely related to hæmochromogen is found widely distributed in almost all tissues of animals and plants, and has been given the name cytochrome by Keilin. It exists in the oxidised and reduced forms, the latter of which shows a characteristic spectrum (Fig. 335). In living tissues examined by the microspectroscope the formation of the reduced

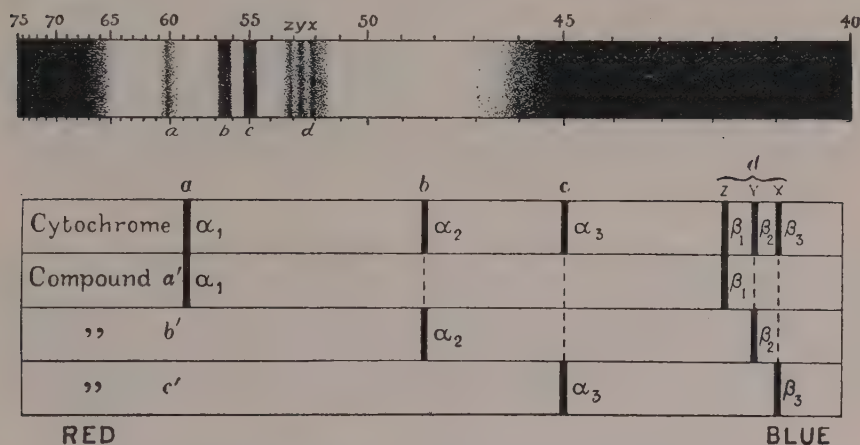


FIG. 335. Above : Absorption Spectrum of Cytochrome in Muscle of Bee. Reduced form as obtained by crushing tissue between two glass slips.

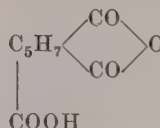
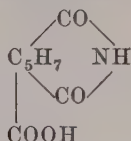
Below : Showing the three separate hæmochromogen spectra which together make up the above spectrum of cytochrome. (Expanded scale.) (BARCROFT, after KEILIN.)

cytochrome can be witnessed when oxygen is excluded, and it seems probable that cytochrome plays some important part in the transfer of oxygen from the blood to the tissues. It functions, in fact, as a peroxidase and gives reactions as such. When oxygen is excluded, the tissues reduce it; when oxygen is readmitted it is oxidised again. The amount of cytochrome in a tissue is closely related to the intensity of its respiration; moreover, when cyanide is added to the tissue, the cytochrome remains in the reduced state even when oxygen is allowed access to it, and at the same time the oxygen utilisation of the tissue is stopped. Cytochrome appears to be a mixture of various modified hæmochromogens (Fig. 335).

Hæmatoporphyrin. If hæmoglobin, hæmatin or hæmin be mixed with concentrated sulphuric acid, it dissolves, forming a purple-red solution. On pouring this solution into a large quantity of water, hæmatoporphyrin is thrown down in the form of a brown precipitate. In order to prepare hæmatoporphyrin, pure crystallised hæmin is added to a saturated solution of hydrobromic acid in glacial acetic acid. The whole is allowed to stand for three or four days and is then thrown into distilled water. The resulting

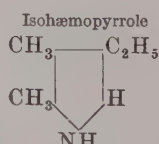
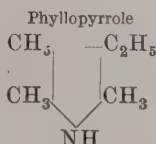
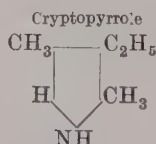
mixture is filtered and the hæmatoporphyrin thrown down by careful neutralisation of the hydrobromic acid with caustic soda. Hæmatoporphyrin is easily soluble in alkalis and somewhat less readily so in acids, forming alkaline and acid hæmatoporphyrin respectively. According to Willstätter its formula is $C_{34}H_{38}N_4O_6$. An alcoholic solution of hæmatoporphyrin acidulated with hydrochloric acid shows two absorption bands: one, the fainter, between C and D; and the other, broader and more defined, midway between D and E. Solutions of alkaline hæmatoporphyrin show four absorption bands: a weak band between C and D; another between D and E; a more strongly marked band nearer to E; and a fourth band, darkest of all, between *b* and F. It will be observed that, in the formation of hæmatoporphyrin from hæmatin, the iron of the latter has been split off by the action of the strong acid. Laidlaw has found that the splitting off of iron occurs much more readily in the absence of oxygen. If reduced hæmoglobin be taken, or defibrinated blood which has been allowed to stand until it is thoroughly reduced, it is sufficient to add 15 per cent. hydrochloric acid in order not only to convert the greater part of the hæmoglobin to hæmatin but to split off the iron of the latter and form hæmatoporphyrin. Hæmatoporphyrin occurs in minute quantities in normal urine and in larger quantities in certain toxic conditions, especially in poisoning by sulphonal, when the urine may have a bright purple colour. It is important to remember that, although urine is acid from the presence of acid sodium phosphate, urinary hæmatoporphyrin is always alkaline hæmatoporphyrin and gives the spectrum of this body.

CHEMICAL RELATIONSHIPS OF HÆMATIN. Hæmatin is widely diffused through the animal kingdom, occurring in the form of hæmoglobin in a large number of the invertebrata, as well as in all the vertebrata except perhaps *Amphioxus*. When hæmatin is oxidised with sodium bichromate and acetic acid, two new acids are formed, called the hæmatinic acids. One of these has the formula $C_8H_9O_4N$, and the other $C_8H_9O_5$. The first acid is converted into the second by the action of alkalis. The relationship of the two hæmatinic acids can be represented by the following formulæ:



If, on the other hand, hæmin or hæmatoporphyrin be reduced by the action of hydriodic acid dissolved in acetic acid with the addition of phosphonium iodide, and the product be distilled with steam, the distillate contains a mixture of substituted pyrroles formerly known as hæmopyrroles. The mixture readily oxidises to a red substance on exposure to the air. If ammonia be added to the coloured solution, the colour changes to yellow which, on the addition of an ammoniacal solution of zinc chloride, changes to pink with a green fluorescence. These reactions are also given by urobilin, one of the urinary pigments and the chief pigment of the fæces, as well as by hydrobilirubin, a substance obtained by the action of tin and sulphuric acid on an alcoholic solution of hæmatin.

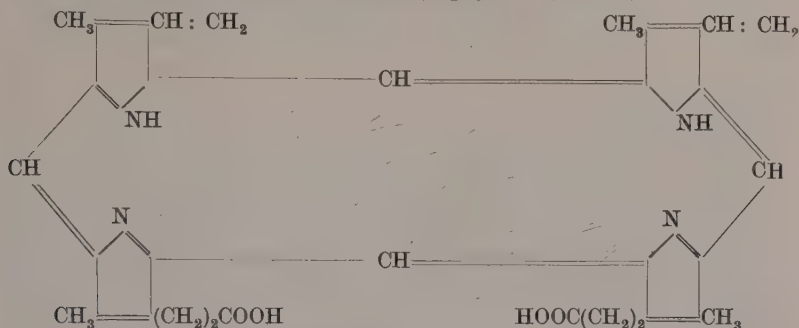
The hæmopyrroles, according to Willstätter, are three in number and have the following formula:



The same substances can be obtained from the chlorophyll of plants.

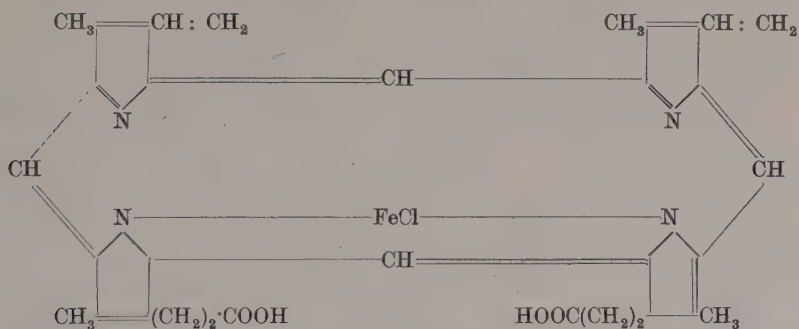
Thus the same group forms the basis both of the substance which is responsible in the plant for the assimilation of carbon from carbon dioxide, and of the pigment which in the animal is the carrier of oxygen between the tissues and the surrounding medium. These and various other pigments found in animals and plants belong to the chemical group of *porphyrins*, which consist of four substituted pyrrol rings. Hæmatoporphyrin may be taken as a type.

A possible structural formula for hæmatoporphyrin is (Fischer) :



The porphyrins exist in various metallic derivatives, called *metallo-porphyrins*, of which hæmatin and its derivatives are examples. Many porphyrins are known and some have been synthesised; all the porphyrins form the corresponding iron-porphyrins when treated with ferric chloride and sodium acetate.

The following is a suggested formula for hæmin (H. Fischer and Zeile) :



Metallo-porphyrins containing other metals than iron are also known to occur naturally, *e.g.* turacin, a feather pigment containing copper; and compounds containing cobalt, nickel, zinc, &c., have been artificially prepared. Again, iron porphyrins in which the porphyrin part is different, *e.g.* the respiratory pigment chlorocruorin, found in certain worms, have recently been subjected to study.

THE SYNTHESIS OF THE BLOOD PIGMENTS. Many of the porphyrins can be made synthetically and H. Fischer and his pupils have recently (1929) succeeded in synthesising hæmatoporphyrin, hæmatin and hæmin. Given hæmatoporphyrin, moreover, Laidlaw showed that the iron could easily be introduced, and hæmochromogen prepared, and from this hæmatin.

One gramme of hæmatoporphyrin is dissolved in dilute ammonia and warmed in a flask on the water-bath. Some Stokes' fluid, prepared from about 2 grammes ferrous sulphate, and a few drops of a 50 per cent. hydrazine hydrate solution are added. At the end of one or two hours the solution is seen to be of a bright red colour when examined in thin layers, and on dilution shows the typical absorption spectrum of hæmochromogen, which changes to that of alkaline hæmatin on shaking with air. Strong potash is added, and the ammonia is boiled off in an evaporating dish with free exposure to the air.

The hydrazine is decomposed, and a solution of hæmatin remains which can be precipitated by acidification with hydrochloric acid. The pigment obtained in this way agrees in every respect with that prepared from oxyhæmoglobin. Analysis of the product gave 9.58 per cent. of iron, which agrees with Nencki's formula for hæmatin, $C_{32}H_{30}N_4O_3Fe$.

The pigment called turacin, occurring in the wing feathers of certain birds, was shown by Church to contain copper and to yield, on treatment with strong sulphuric acid, a substance indistinguishable from hæmatoporphyrin. Laidlaw also succeeded in synthesising this pigment by treating hæmatoporphyrin with ammoniacal copper solution, showing that it is a compound corresponding to hæmatin, in which the place of iron is taken by copper.

Various claims have been made in the past to have prepared hæmoglobin, but these investigations were carried out before the nature of hæmochromogen and its relation to hæmatin were fully understood. Recently, however, R. Hill and Holden succeeded. They prepared globin from oxyhæmoglobin without denaturation, by treating oxyhæmoglobin solutions with the smallest requisite amount of HCl. at $-2^{\circ}C$. to form acid hæmatin; this was removed, and the globin after further purification was mixed with hæmatin in sodium carbonate, when methæmoglobin resulted. This on reduction gave reduced hæmoglobin, which on shaking with air gave oxyhæmoglobin, recognisable by its absorption spectrum. If denatured globin is employed, hæmochromogen is formed instead of methæmoglobin.

THE LIFE-HISTORY OF THE RED BLOOD CORPUSCLES

In the very earliest stages of the embryo there is no vascular system, the cells being nourished by diffusion from cell to cell. At a very early stage of development there arises from the mesoderm in various situations the primitive connective tissue, or *mesenchyme*, and it is in this tissue, or from its direct descendants, that both blood cells and vessels are developed.

The first appearance of blood cells is in mesenchyme tissue situated outside the embryo itself, in the *area opaca* of the yolk sac, and in the amnion and chorion. Here are formed the blood islands, groups of cells in which the peripheral mesenchyme cells form the endothelium of the vessels, an intercellular fluid, the plasma, and the more centrally placed cells, the *primitive blood cells*, all of which latter are nucleated cells which closely resemble the parent mesenchyme cells. In man the earliest vessels appear in this way on the under-surface of the yolk sac, and gradually extend over its surface, finally establishing connection with the similar vessels of the chorion. By the third week communication has been established between this system of vessels and another system of vessels, namely the blood vessels and heart, of the embryo itself. The vessels of the embryo are likewise developed from the mesenchyme, but with the difference that in these vessels the differentiation of the mesenchyme is into *endothelium* and plasma only, with practically no primitive blood cells. The first blood cells in the embryonic circulation, therefore, represent an invasion of primitive blood cells from the yolk sac vessels into the vascular system of the embryo, when connection has been established between the two systems.

The primitive blood cells undergo further differentiation, and from them are derived cells called *hemocytoblasts*. These cells are the primitive stem cells from which, according to some authorities, all the cells of the blood are ultimately derived. In the formation of the red cells, these cells are converted into the immediate precursors, called *erythroblasts*, and from these, by the formation of hæmoglobin, into the fully formed red cells.

In the foetus the cells reach the circulation in an immature form and are nucleated, but in the adult all the corpuscles are of the non-nucleated type. They are formed in the adult in the red marrow of the bones, and can be shown to be derived from nucleated erythroblasts by a process of degeneration and

solution of the nucleus (Fig. 336). The formation of red corpuscles does not cease with the end of foetal life or even with the attainment of full stature by the animal. We have definite proof that a continual formation of red corpuscles can proceed, and is proceeding, throughout the whole of adult life. In an adult the total number of corpuscles remains approximately constant. By bleeding an animal we can diminish the total amount of corpuscles. The first effect of such a bleeding is that the fluid parts of the blood are made up, so that the volume of the blood is restored to normal and the blood therefore



FIG. 336. Part of a Blood Vessel from the Yolk Sac of a Rabbit Embryo, showing the Changes which occur in the Formation of Erythrocytes. (From SCHAFER after MAXIMOW.)

- | | |
|--|---|
| a. Megaloblasts. | en. Phagocytic endothelial cells. |
| b. Normoblasts, changing into erythroblasts. | l. Lymphocytes. |
| c. Erythroblasts, in which the nuclei are disappearing. | k. A divided lymphocyte. |
| d. An erythrocyte fully formed, but not yet disc-shaped. | n. Erythroblasts, shrunken, and with trophic nucleus. |

becomes relatively poor in corpuscles. In a few weeks, however, the corpuscular content of the blood is found to be once more normal, showing that the loss of corpuscles has been followed by a compensatory regeneration. The fact that the pigments constantly leaving the body with the urine and faeces, namely, urochrome, urobilin and stercobilin, are derived by means of the liver from hæmoglobin, shows that a constant destruction of red corpuscles must be proceeding. Since the number of corpuscles remains unaltered, this loss of hæmoglobin must be made good by a continual regeneration of fresh hæmoglobin and new red corpuscles. That the marrow is involved in the process is shown by the fact that it is the only tissue of the body which

undergoes an alteration in appearance when blood formation is stimulated by such means as repeated bleeding or destruction of corpuscles by the injection of toxic agents. Under such conditions the red marrow, which in adult mammals is present only in the epiphyses, is found to have increased in extent and in many cases to occupy the greater part of the shaft of the bone, having taken the place of the yellow marrow. It is in the red marrow, therefore, that we must seek the precursors of the red blood corpuscles.

In the bird the erythroblasts, *i.e.* the precursors of the nucleated red blood corpuscles, form a sort of inner lining to the dilated capillaries of the marrow (Fig. 337). Here we can see all grades between the colourless nucleated corpuscle which lies nearest the periphery and the adult red oval corpuscle containing hæmoglobin, lying next the lumen and ready to be carried away in the blood stream. If blood formation has been stimulated by repeated bleeding, this blood-forming tissue occupies the greater part of the lumen of the mar-

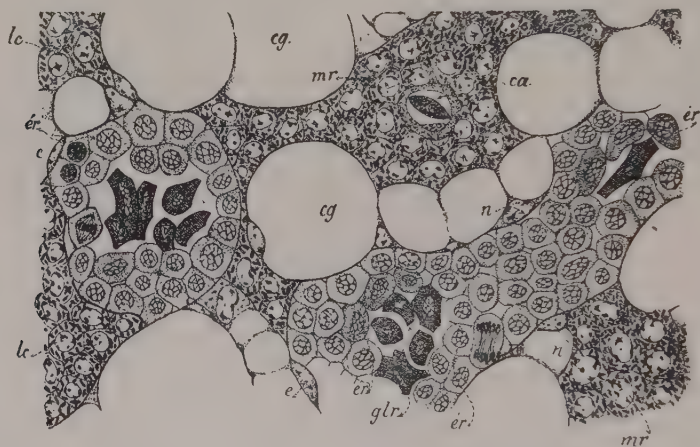


FIG. 337. Section of Red Marrow of Pigeon. (DENYS.)

- | | |
|---|---|
| lc. Eosinophile leucocytes. | ca. Blood capillary. |
| cg. Fat cells. | er. Erythroblasts lying within vascular |
| e. Nucleus of endothelial cell of blood | endothelium. |
| vessel. | glr. Fully formed red corpuscles. |

row capillaries. If, however, blood formation has been reduced to its lowest extent by a process of chronic starvation, the erythroblasts form a single layer of cells just inside the dilated capillaries, and intermediate stages between the erythroblasts and the fully developed erythrocytes are almost entirely wanting. In the frog this process of blood-corpuscle formation occurs only at one period of the year, in the early summer, and it is only at this time that the bones are found to contain red marrow.

In mammals the process is very similar. The hæmoglobin-containing cells are often to be seen in process of division, and the nucleated daughter-cells appear to undergo a process of nucleolysis, the nucleus being extruded or dissolved. When blood formation is quickened as the result of previous destruction or loss, some of these immature nucleated blood discs may make their way into the circulation and be found in the blood, where they are spoken of as *normoblasts*. Other young, though non-nucleated, cells (reticulocytes) can also be distinguished by the fact that they stain with polychrome methylene blue, while the older erythrocytes do not.

The fact that the rate of formation of new red cells keeps pace with the

rate of their destruction, indicates that there must be some stimulus which acts appropriately on the red marrow. We do not know what the nature of this stimulus is, but some facts suggest that it may be of a chemical nature and may emanate from the liver. For instance, Whipple, and Minot and Murphy discovered that feeding with raw liver has a most beneficial effect in pernicious anæmia, in which new erythrocyte formation appears to be deficient, and Cohn has found that extracts of liver having the same effect can be prepared.

How long a corpuscle continues to exist in the circulating blood is not known with certainty, though there are indications that, in man, the average life of the corpuscle is about three weeks. Sooner or later, however, every corpuscle undergoes disintegration, a process generally ushered in by the ingestion of the corpuscle by some phagocyte cell. Thus, in the hæmolymp glands and in the spleen, we find large reticulo-endothelial cells which have englobed red corpuscles and in which we can recognise pigment granules derived from their destruction. The chief places of disintegration of the hæmoglobin are certainly the liver and spleen, and in these organs the hæmoglobin is converted into bilirubin, which is then excreted by the liver. The liver cells themselves do not form bilirubin, but merely excrete the bilirubin which is formed in the various cells of the reticulo-endothelial system. Injection of hæmoglobin into the circulation causes increased secretion of bile pigment. A section of normal liver immersed in potassium ferrocyanide and then in acid alcohol shows the presence of iron by the assumption of a blue colour. The amount of iron which can be demonstrated in the liver in this way is enormously increased in any condition which augments the rate of blood destruction. In the pathological condition known as pernicious anæmia, as well as after poisoning by the injection of pyrogallie acid or toluylene diamine, both of which agents cause a great destruction of red blood corpuscles, the liver on treatment in this way takes on a deep blue colour. In the destruction of the corpuscles, the hæmoglobin is dissociated first into its protein and chromogenic moieties; the hæmatin then loses its iron and is converted into bile pigment. The iron remains in combination in the liver, and is probably utilised for the formation of the fresh hæmoglobin in the bone marrow.

That the liver is by no means the sole seat of bile pigment formation is shown by the results of experiments by Whipple, F. C. Mann and their colleagues. The latter find that the liver can be completely removed from dogs, provided sufficient glucose is given to prevent the occurrence of hypoglycæmic symptoms (see Chapter XXX.); ten hours or less after removal of the liver definite jaundice develops, and the urine, blood plasma and adipose tissue are stained with bilirubin. The jaundice is increased if hæmolysed blood is injected.

Bilirubin is present in small amount in normal blood plasma, but in jaundice the amount is largely increased. Its presence can be demonstrated by the *van den Bergh reaction*. In this test, the serum is precipitated with alcohol and the filtrate added to a freshly prepared mixture of sulphanilic acid, hydrochloric acid and sodium nitrite, when a violet-red colour is produced.

THE BLOOD PLATELETS

If a drop of osmic acid be placed on the finger, which is then pricked through the drop so that the shed blood may mix with the fixing fluid directly it leaves the vessels, a drop of the mixture when examined under high powers is seen to present a number of granular bodies from one-third to one-half the diameter of a red blood corpuscle. Their number has been variously stated to

be from 180,000 to 800,000 per cubic millimetre. Their shape varies considerably. Some are bi-convex structures; others are flatter with numerous processes. They may be isolated or agglutinated into clumps. Their shape, size, and number vary according to the method adopted for their demonstration.

When blood is examined in Hayem's fluid * nearly all the blood platelets appear as bi-convex discs. The best method for the display of platelets is apparently that given by Deetjen. The drop of blood is received directly from the vessels on to a sheet of solid agar jelly which is made with 0.6 per cent. sodium chloride solution with the addition of sodium metaphosphate and dipotassium phosphate. When examined on this medium large numbers of platelets are seen, each of them provided with numerous processes (Fig. 338). Their central part is more strongly refracting than the periphery and stains with basic dyes, so that it has been regarded as a nucleus.

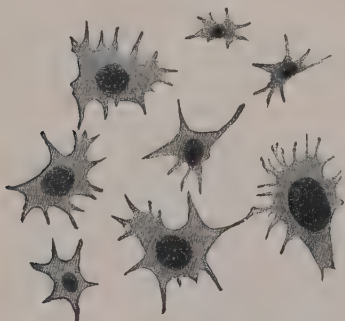


FIG. 338. Blood Platelets, highly magnified, showing the amoeboid forms which they assume when examined under suitable conditions, and also exhibiting the chromatic particle which each platelet contains, and which has been regarded as a nucleus. (After KOPSCHE.)

Similar platelets are observed when the blood is received into normal salt solution; as the mixture clots, the filaments of fibrin can be seen often to radiate from a disintegrated blood platelet as from a centre. That the blood platelets are concerned in the production of clots is shown by the fact that in the living vessels blood platelets aggregate round any injured spot in the vessel wall, and later fuse together so as to form an adherent thrombus or clot which covers the seat of injury and helps to repair the damage and to prevent the escape of the contents of the blood vessel. If the blood of an animal be defibrinated by repeated bleed-

ing, whipping and returning to the veins of the animal, it will be found for the next few days to be quite free from blood platelets. Most histologists regard the platelets as derived by fragmentation from the cytoplasm of the giant cells, or megakaryocytes, of the bone marrow. According to Buckmaster, however, a film of blood examined in a platinum loop, and kept carefully at the temperature of the body, presents no platelets on microscopic examination, so that he, and some other investigators, regard them as artefacts.

THE COAGULATION OF THE BLOOD

In the process of coagulation, while the corpuscles remain to a large extent intact, the plasma becomes solid from the production in it of a network of fibrin. The question of coagulation involves the consideration of the precursors of fibrin and of the conditions which determine their conversion into fibrin. It is evidently impossible directly to arrive at any conclusions on these points during the few minutes which elapse before the appearance of the clot. We must therefore find some means of retarding coagulation, so that we may obtain the plasma free from corpuscles and be able to initiate

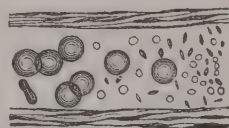


FIG. 339. Blood Corpuscles and Blood Platelets within a small Vein. (SCHAFER after OSLER.)

* Hayem's solution:

Mercuric chloride	0.5 grm.
Sodium sulphate	5.0 grm.
Sodium chloride	2.0 grm.
Distilled water to	200 c.c.

coagulation in this cell-free fluid at will. Having succeeded in staying the process of coagulation, it is always possible to obtain a cell-free plasma by the employment of a centrifugal machine, by which the corpuscles are thrown rapidly down to the bottom of the tube and the clear supernatant plasma can be syphoned off.

METHODS OF PREVENTING COAGULATION

(1) So long as the blood is in contact with the uninjured vessel it remains fluid. If the jugular vein of an animal be tied in two places, the blood contained between the ligatures will remain fluid, sometimes for days. If the tube of vein be hung up, the corpuscles sink to the bottom and the plasma in the upper part of the tube can be poured from one vein to another without undergoing coagulation. On pouring it into a glass vessel or bringing it into contact with foreign substances, it undergoes coagulation.

(2) When an incision is made in the ordinary way into a blood vessel of a bird, the issuing blood clots very rapidly. The clotting is initiated by a substance contained in the tissues surrounding the vessels. If, therefore, the vessel be isolated and a perfectly clean glass cannula be inserted into it, care being taken not to bring the cannula in contact with any of the surrounding tissues, blood can be drawn off into a sterilised beaker perfectly free from dust and will remain unclotted for days. Such blood can be centrifuged and the cell-free plasma used for experiment. The same procedure does not apply to the mammal, where even the most scrupulous care to prevent contamination by the tissue juices will not prevent the blood from clotting on leaving the vessels.

(3) Clotting can be excited even in the living vein by introducing into the blood any solid substance, *e.g.* a thread, which is wetted by the blood. If the contact of shed blood with such substances be prevented by receiving it into vessels previously coated with oil or with paraffin, and scrupulously free from dust, clotting may often be delayed for many hours.

(4) Cooled plasma. Horses' blood is received directly into a narrow vessel immersed in ice, so as to cool it rapidly to between 0° C. and 1° C. At this temperature it remains fluid for an indefinite time. The corpuscles sink, and the supernatant plasma can be decanted and filtered.

(5) *Methods involving Mixture with Neutral Salts.* Blood from any animal is received into one-quarter its bulk of a 25 per cent. solution of magnesium sulphate, or into an equal volume of half-saturated sodium sulphate solution. The plasma obtained in either of these ways is known as salt plasma. Clotting is indefinitely delayed in either case, but it can be induced by suitable treatment of the separated plasma.

(6) *Methods depending on Decalcification of the Blood.* Oxalate plasma is obtained by receiving blood into a solution of sodium oxalate so that the total blood contains 0.1 per cent. of the oxalate. Instead of oxalate we may use sodium fluoride (0.3 per cent.) or sodium citrate (0.25 per cent.).

(7) *Methods depending on the use of certain Substances of Animal Origin.* (a) *Peptone plasma* is obtained by injecting rapidly into the veins of a dog or cat in a fasting condition a solution of commercial peptone in the proportion of 0.1 gramme peptone per kilo. of the animal. The effect of this injection is to cause a rapid fall of blood pressure and hurried respiration, and the animal then passes into a state of coma and shock which may last an hour or two. On drawing off the blood immediately after the fall of pressure has taken place, it is found to be uncoagulable, and cell-free plasma can be obtained from it by the use of the centrifuge. A number of animal extracts act in a somewhat similar fashion, such as extract of crayfish, of mussels, &c. The addition of peptone to blood drawn into glass vessels does not inhibit clotting, but if contact with glass is avoided by the use of paraffined cannulæ and vessels, then concentrations of peptone not much larger than those given intravenously will greatly retard coagulation. (Pickering and Hewitt.)

(b) *Leech Extract or Hirudin Plasma.* It has long been familiar that the bites made by leeches continue to bleed for a considerable time, and it was shown by Haycraft that this is due to the presence of an anticoagulating substance in the buccal glands of the leech. This substance, which has the properties of an albumose, can be extracted by boiling from the anterior half of the leech. It will abolish the coagulability of the blood either when injected into the blood stream or when blood is received into a solution of hirudin *in vitro*.

(c) *Heparin.* An anticoagulant substance, to which the name of heparin has been given, has been prepared from dog's liver by Howell. When purified it appears to be a

derivative of glucuronic acid, and 1 mg. will prevent coagulation of 100 c.c. of blood. It acts equally well *in vivo* or *in vitro*.

By any of these methods it is possible to obtain blood plasma free from formed elements. The conditions which will bring about coagulation in such plasmata are strikingly diverse. Thus in cooled plasma a rise in temperature is sufficient to bring about coagulation. If, however, the cooled plasma be filtered several times through two thicknesses of filter-paper, being kept at a temperature of about 1° C. during the whole time, it loses this spontaneous coagulability on warming. It can still be made to clot by the addition of certain substances such as blood serum or the washings of a blood clot, and in some cases by the addition of tissue extracts. Oxalate plasma clots on addition of calcium salts. Sodium sulphate plasma clots on dilution. Magnesium sulphate plasma will not clot on dilution, but needs in addition the presence of some blood serum or some substance derived from blood serum. In both these cases tissue extracts have no influence.

By a careful study of these forms of plasma we can arrive at a conception of the processes of coagulation. We may take as our type oxalate plasma. This is a clear yellow fluid perfectly free from formed elements, which evinces no tendency to clot. On adding a drop of calcium chloride to such plasma, we see that it contains an excess of oxalate from the production of a precipitate of calcium oxalate. If calcium chloride be added drop by drop so as to be present in slight excess, and the plasma be then kept warm, it will clot within a time varying from a few minutes to an hour. The clot thus formed is perfectly firm, though very often no retraction of the clot takes place. The place of calcium can be taken by strontium, but barium and magnesium are powerless to initiate clotting. We must therefore conclude that the presence of a soluble calcium salt is one factor necessary for coagulation. This is borne out by the fact that a similar uncoagulable blood is produced by the action of sodium fluoride, which also precipitates calcium, and by sodium citrate, which, as shown by Sabbatani and C. J. Martin, leads to the formation of a salt of sodium calcium citrate, in which the calcium is in the complex anion, the cation being sodium. This shows that for calcium to exercise its function in clotting, it should be present in a form which yields calcium ions.

A second factor in coagulation is the mother-substance of fibrin. If the composition of the plasma, before coagulation, be compared with that of the serum which has separated from the clot, it is found that plasma contains a protein, *fibrinogen*, not represented in the serum, which must therefore be the precursor of fibrin. Fibrinogen is a globulin which can be separated from oxalate plasma by half-saturation with sodium chloride or one-quarter saturation with ammonium sulphate. An equal volume of a saturated solution of sodium chloride is added to plasma so that the whole mixture contains 16 per cent. sodium chloride. The fluid gradually becomes turbid from the production of a precipitate which, at first granular, rapidly aggregates to form a stringy, slimy solid, which adheres to the glass rod used for stirring. This mass can be taken out of the fluid, washed by kneading with half-saturated sodium chloride solution, and then redissolved by the addition of distilled water. With the salt adhering to the precipitate a dilute saline fluid is formed in which the fibrinogen is soluble. Fibrinogen is also soluble in dilute alkali, from which it is re-precipitated by acidification. The fibrinogen can be purified by repeating the precipitation and solution, though it tends to lose its solubility in the process, so that purification is always attended with some loss. The solution of fibrinogen thus obtained is perfectly clear and colourless. On heating, it coagulates between 56° and

60° C. The same precipitate is produced on heating the original plasma, whereas serum does not give any precipitate at 60° C.

A third factor, called *thrombin*, is also involved in clotting. If a solution of fibrinogen, obtained by precipitating with sodium chloride and dissolving in distilled water, be treated with a drop or two of calcium chloride, it rapidly clots with the formation of fibrin. We might conclude from this experiment that fibrin was a compound produced by the union of calcium salts with fibrinogen. Further experiments however show the untenability of this hypothesis. If the fibrinogen has been thoroughly purified by repeated precipitation and re-solution, calcium salts are found to have entirely lost their power of causing coagulation. Such a purified fibrinogen can still be made to clot by the addition either of serum or of the washings of a blood clot, or of the watery extract of alcohol-coagulated serum. This power of serum to convert fibrinogen into fibrin is due to the presence in it of minute quantities of a substance which has been designated as thrombin. It was formerly regarded as an enzyme because it is active in minimal quantities. Thus if we add some serum to a fibrinogen solution we can cause clotting, and then on squeezing the clot obtain a serum which will bring about coagulation when added to a fresh portion of fibrinogen. Rettger and Howell have, however, demonstrated that thrombin does not fulfil the requirements of an enzyme. If small quantities of thrombin solution be added to large quantities of plasma or of pure solutions of fibrinogen, the amount of fibrin obtained is proportional to the amount of thrombin added. This is shown in the following experiment :

5 drops of thrombin gave 0.2046 gramme fibrin.					
10	"	"	0.3573	"	"
20	"	"	0.6089	"	"
40	"	"	1.5872	"	"

Moreover, the action of thrombin on fibrinogen solutions is almost independent of temperature, occurring practically as rapidly at 17° C. as at 40° C. Rettger therefore regards fibrin as formed by the *union* of thrombin and fibrinogen. This union is apparently very unstable. If fibrin be extracted with 8 per cent. salt solution for some time, the solution is found to contain thrombin. It may be further purified by shaking with chloroform and evaporation to dryness at 40°, and then gives the reactions of a protein. Its potency is, however, not reduced by tryptic digestion, but increased. Thrombin can also be re-extracted from fibrin if the latter be allowed to putrefy.

From all the different kinds of plasma enumerated above, fibrinogen can be obtained by the use of sodium chloride, and in every case can be made to clot by the addition of serum or of a solution of thrombin. The last change in the act of clotting is therefore the change from fibrinogen to fibrin, and this event is brought about by the intervention of thrombin. It cannot be at this stage of the process that the calcium salts exercise their influence, since thrombin will cause the coagulation of oxalate plasma.

Thrombin may be provisionally defined as a substance capable of producing clotting in fibrinogen solutions. Accepting this definition, we can employ fibrinogen solution as a reagent for thrombin. By this means we can show that thrombin is absent from circulating blood. If blood be received direct from the vessels into absolute alcohol and the precipitate, after coagulation by alcohol, be extracted by water, the extract is found to contain no trace of thrombin. The same statement applies to fresh oxalate plasma. If however oxalate plasma be made to clot by the addition of calcium salts, the serum squeezed from the clot is found to contain thrombin. In the

process of coagulation, therefore, not only is there a conversion of fibrinogen to fibrin, but there is an actual formation of thrombin. Our next step, therefore, must be to inquire into the precursors of the thrombin and the conditions of its formation.

If oxalate plasma be cooled to 0° C. for two or three days, a scanty granular precipitate is produced. This consists largely of *débris* from platelets, which can be centrifuged off or separated by filtration through a Berkfeld filter. It is then found that the remaining plasma can no longer be made to coagulate by recalcification, although it still contains fibrinogen, which is converted into fibrin on the addition of thrombin. If the precipitate be collected and treated with calcium chloride and the mixture added to the oxalate plasma, the latter clots. But if the precipitate is freed from adherent contamination, it will not clot pure fibrinogen, according to Mills. We must conclude that the precipitate, though itself not thrombin, will give rise to thrombin on treatment with plasma and lime salts. It was therefore regarded by Hammarsten as the precursor of thrombin. This is incorrect, and it is probably safer to call it *thromboplastic material*; but its importance in clotting is beyond question.

Thus far practically all workers on the subject are agreed. Coagulation of the blood is due finally to the interaction of thrombin and fibrinogen. The fibrinogen is present as such in the circulating plasma. Thrombin is not free in the circulating blood, but is produced or liberated after the blood has been shed. For the production of thrombin the presence of calcium salts is necessary. Further research on the nature of the formation of thrombin has shown that the matter is not quite so simple as imagined by Hammarsten.

Oxalate plasma, which has been separated from the precipitate of platelets, can be made to coagulate by the addition of calcium salts together with extracts of almost any animal tissues, and these were therefore supposed to contain thromboplastic material similar to that obtained by cooling oxalate plasma. These extracts, even on mixture with calcium, are without effect on pure solutions of fibrinogen, and moreover, the precipitate produced by cold, if thoroughly washed before treatment with calcium salts, loses its power of evoking coagulation in fibrinogen solutions. The thromboplastic material is therefore unable by itself, even on addition of calcium salts, to produce thrombin, but needs the co-operation of some other substance, which is contained in oxalate plasma and which generally adheres in sufficient quantities to the platelet precipitate.

Three factors are therefore necessary for the production of thrombin: first, calcium salts; secondly, a substance present in the platelets as well as in most animal tissues; and thirdly, a substance present in solution in oxalate plasma. These two latter substances have been respectively designated *thromboplastic material* and *prothrombin*. Thromboplastic material can be obtained by extraction of the stroma of the red blood corpuscles, or of the bodies of lymph cells or leucocytes. It has been shown by Howell that the phosphatid *cephalin* is an essential constituent of thromboplastic material, in which it probably occurs in association with a protein. Similar thromboplastic substances are present in nearly all tissues, and are set free when the cells are injured. Separation of the blood platelets by cooling and filtration abolishes the spontaneous coagulability of any form of plasma. The prothrombin is contained in solution in oxalate plasma. It is therefore concluded that when blood leaves the vessels there is a disintegration of the blood platelets, with the liberation of thromboplastic substance. This acts upon prothrombin in the presence of lime salts and produces thrombin. By the intermediation of the thrombin, the fibrinogen also present in solution

in the plasma is converted into fibrin. The changes occurring in shed blood and resulting in the production of a clot are therefore mainly concerned with the production of thrombin.

This view of the essential characters of coagulation is borne out by observations on other forms of plasma, especially of plasma of birds' blood. This, when obtained with scrupulous cleanliness, so as to avoid any contamination with dust or with the tissues, remains permanently uncoagulable. In the plasma got by centrifuging the blood, no blood platelets are to be seen, and no precipitate is produced by exposure to a temperature of 0°C . We may say, therefore, that blood platelets with their contained thromboplastic substance are absent from such plasma, and with them the property of spontaneous coagulability. It is also free from thrombin, but contains prothrombin as well as soluble calcium salts. It is only necessary to add thromboplastic material in the shape of a watery extract of any tissue, or cephalin, in order to cause the appearance of thrombin and the conversion of the fibrinogen already present in the plasma into fibrin.

In every case the initiation of the act of clotting would seem to depend on the setting free of thromboplastic material in the plasma. In mammalian blood, although this can be derived from red or white corpuscles, we have no reason to believe that there is any appreciable disintegration of these formed elements when the blood leaves the vessels. In oxalate blood, leucocytes can be seen alive, and displaying amœboid movements, two or three days after the blood has left the vessels. Certain observers have assumed the presence of explosive corpuscles which break up directly the blood leaves the vessels, but the existence of such corpuscles in the higher animals has not been demonstrated, though in some invertebrata they are certainly present. The sole source of the thromboplastic material is therefore the very perishable blood platelets, and the first act in coagulation is probably the disintegration of the blood platelets, with the setting free of thromboplastic substance.

The part played by the platelets in coagulation is of great importance in maintaining the integrity of the vascular system. If a fine needle be thrust through the wall of a venous capillary which is kept under observation by the microscope, it will be seen that the blood, as it flows past the injured spot, deposits blood platelets on the side of the puncture. These aggregate to form a plug closely adherent to the wall of the vessel, and effectively preventing any escape of its contents. The blood platelets fuse to form a mass of fibrin, and later on, by the growth of the adjacent endothelial cells, the thrombus is organised, converted into connective tissue, and covered with a layer of endothelium continuous with the rest of the vessel. The same process occurs when any part of the lining membrane of a large vessel is injured. Thus, destruction of a patch of endothelium in a vein leads to the deposition of blood platelets over the patch and the formation of a 'thrombus' adherent to the wall. From this thrombus coagulation may spread through the rest of the contents of the vessel and produce thrombosis of the whole vein. Under healthy conditions the thrombus serves simply to cover the bare area in the wall of the vein, and is grown over later by endothelium, so restoring the integrity of the vessel wall.

Why does the blood not clot in the vessels? No theory of coagulation can be satisfactory which does not account at the same time for this. One factor at any rate in the prevention of intravascular clotting must be the nature of the surfaces with which the blood comes in contact. The blood, even of mammals, can be prevented for a time from clotting if it be kept carefully from contact with any foreign substance which is wetted by it, as for

instance, when it is received into vessels free from dust and coated with a layer of oil or paraffin. On the other hand, free contact with such substances, as occurs when the blood is whipped, materially hastens the process of coagulation. One must therefore conclude that mere contact with a foreign body has a direct destructive action on the blood, leading to the disintegration of blood platelets and the discharge of thromboplastic substance. In birds, the platelets, or the plasma colloids, or both, are more stable than in mammals, so that coagulation is held in abeyance if contamination with the juices of damaged tissues is avoided. But birds' blood can be made to clot without the addition of tissue juice if, by increasing the mechanical insult, as by violent whipping, filtration through a clay cell, or addition of water or chloroform, we destroy the formed elements, so leading to the liberation of their contained thromboplastic material.

Many physiologists believe that another factor which plays an important part in the maintenance of fluidity within the circulation, is the presence in the blood of an anticoagulant substance, such as the heparin of Howell. This substance can prevent the formation of thrombin, though unable to inhibit the action of this when once it has been formed. It is therefore an anti-prothrombin. Others believe that an anti-thrombin (akin to hirudin, but differing from it in being thermolabile), is present normally in the circulating blood, and in excessive amount after the injection of peptone; this substance neutralises the action of thrombin, and is believed, like heparin, to be formed in the liver and perhaps also in the vascular endothelium generally. Although evidence of the existence of these bodies is still somewhat uncertain, the fact that blood serum often has an inhibitory effect on the action of thrombin points to the presence in the serum of some anti-body. One must assume, too, that processes of disintegration are continually occurring in the blood and involving the plasma, blood platelets and leucocytes, just as we know them to affect the red blood corpuscles. In the healthy animal the liberation of thromboplastic material, which must take place under these circumstances, has no influence in producing clotting. The organism must possess means of neutralising the presence of small quantities either of cephalin or of thrombin. When small quantities of either of these substances are injected into the blood stream, no coagulation takes place, but the blood obtained after the injection clots with *less* readiness than before, a change which can be ascribed to the production, in the body, either of anti-prothrombin or of anti-thrombin. This production of anti-coagulins must be continually taking place and must co-operate in the preservation of the fluid state of the blood while in the vessels.

INTRAVASCULAR CLOTTING. On account of the protective mechanisms with which the animal organism is endowed, the production of clotting in the vessels of the living animal is not readily effected by the injection of thrombin. We have to inject a very strong solution of thrombin, or the strong coagulant contained in the venom of certain snakes, in order to bring about coagulation of the blood in the vessels. Intravascular clotting is more easily caused by the injection of tissue extracts. It was shown by Wooldridge that normal saline extracts of tissues rich in cells, such as the thymus, lymph glands or testis, invariably cause extensive thrombosis. If such extracts be acidified with acetic acid, a precipitate is produced which is soluble in dilute alkalies, and on gastric digestion yields a precipitate rich in phosphorus. Alkaline solutions of the acid precipitate bring about intravascular clotting when injected into the blood stream. According to Wooldridge the injected substance takes part in the formation of the clot, and he

therefore gave it the name of 'tissue fibrinogen.' It is probably a compound of protein with a phospholipide, such as cephalin. The latter, when separated from the protein is thermostable. It is certainly rich in lipides, and the precipitate obtained from it on gastric digestion may contain as much as 25 per cent. of these substances. It must be derived either from the cytoplasm or from the interstitial fluid of the tissues. We may explain the action of these tissue extracts as due to their containing cephalin. Their injection would resemble the liberation of thromboplastic material which normally occurs when blood leaves the vessels, and, according to Howell, their thromboplastic effect is due to their power of neutralising anti-prothrombin (heparin).

More difficult to understand is the result of injecting small amounts of these tissue extracts or larger amounts very slowly. A minute quantity of tissue extract injected into the blood stream produces, not intravascular clotting, but a *delay* in the coagulation time. Repeated injections of small doses may absolutely annul the coagulability of the blood, which will remain unclotted for many days. The same double effect may be observed even with a larger dose. In rabbits, and in dogs after a full meal, the intravascular coagulation which occurs is complete, extending through the whole vascular system. If the injection be made into a fasting dog the thrombosis produced is limited to the portal vein. There is a sudden fall of blood pressure, from which the animal gradually recovers. If a vessel be opened during the period of low pressure, the blood which flows out is totally uncoagulable, and if the animal be killed at this time a clot will be found filling up the whole portal vein. Wooldridge described these two effects of injection of tissue extracts, namely the coagulation and the loss of coagulability, as the *positive* and *negative phases* respectively. Since the negative phase has not been observed in any form of extravascular plasma, we must ascribe it to a reaction on the part of the living cells and probably, since it is so rapid in its establishment, to the action of the cells lining the blood vessels, probably those of the liver. The interest of these observations lies in the relation which they bear to the production of immunity. If a toxin such as that of diphtheria or tetanus be injected into an animal, an antitoxin is produced in the course of two or three days. If now a further dose of toxin be injected, its first effect is to destroy the whole of the antitoxin present in the circulating blood. In the course of a day or two, the antitoxin gradually returns, and at the end of three days is found in the blood in larger quantities than were present before the second injection. Every toxin has, therefore, a positive as well as a negative phase of action. Tissue extracts in their effect on coagulation have a similar positive and negative phase, but these phases are established within a few seconds instead of taking two or three days for their development.

FATE OF THE THROMBIN. The substances which interact for the production of thrombin in shed blood, and thrombin itself, are not entirely used up in the process of clotting. Blood serum, though free from fibrinogen, contains traces of thromboplastic substance (which can be precipitated by the addition of dilute acetic acid) and thrombogen, as well as a fairly strong solution of thrombin. Thrombin, however, rapidly disappears from serum, so that a blood serum which has been kept for two or three days may be almost free from it. Such a serum can be reactivated by the addition of small traces of either acid or alkali. It has been suggested that the thrombin undergoes a modification into an inactive form which is called *metathrombin*. This substance is unaltered by calcium salts or by the addition of thromboplastic material, but can be reconverted into thrombin by means of acids or

alkalies. According to Rettger the disappearance of thrombin from serum is due to its combination with some of the proteins of the serum. This combination, like that of thrombin with fibrinogen to form fibrin, is unstable and can be broken up by the action of alkalies, acids or even of putrefaction. Thrombin itself seems to be extremely stable and will withstand even the temperature of boiling water for a short time. If solutions containing thrombin be evaporated to dryness, the dry residue can be heated to 135° C. without destruction of the thrombin.

We are now in a position to see how far the theory of coagulation evolved from a study of two forms of plasma will serve to explain the behaviour of the many other kinds of plasma which have been the subject of investigation.

COOLED PLASMA contains the thromboplastic material in the form of blood platelets. This precipitate can be separated by centrifuging at a low temperature or by filtration. The remaining plasma contains only thrombogen, calcium salts and fibrinogen, and can be made to clot by the addition of tissue extracts or of thrombin, but will not clot on warming.

IN SODIUM SULPHATE PLASMA the interaction of the fibrin factors is merely impeded by the excess of salt. All are still present, and it is therefore sufficient merely to dilute the plasma in order to produce clotting.

MAGNESIUM SULPHATE PLASMA behaves somewhat differently. If the blood be received directly into magnesium sulphate solution, and the mixture centrifuged while still warm, a clear magnesium sulphate plasma is obtained which will clot on simple dilution. If the blood be left for twenty-four hours before centrifuging, the plasma will not clot on dilution nor on addition of tissue extracts. It contains fibrinogen only, and is therefore an excellent reagent for the presence of thrombin. Magnesium sulphate not only hinders the interaction of the fibrin factors, but actually slowly precipitates the thromboplastic material, so that if time be allowed for this precipitation to be complete the remaining plasma contains only fibrinogen.

SODIUM FLUORIDE PLASMA might be expected to act like oxalate plasma since sodium fluoride is a precipitant of calcium salts. This salt, however, has the additional property of causing a certain amount of fixation of the formed elements of the blood, including the blood platelets. If it be thoroughly centrifuged so that the plasma is obtained free from these constituents, it will no longer clot with calcium salts * nor even with calcium salts *plus* tissue extracts, but will clot readily on addition of thrombin. Although it still contains a certain amount of thrombogen, this is entangled and carried down in the precipitate of calcium fluoride which is produced by the addition of calcium salts, so that the thromboplastic material has nothing on which to exercise its effect. Sodium fluoride plasma is therefore useful, like magnesium sulphate plasma, as a test for the presence of thrombin. If water be added to the sodium fluoride blood, so as to destroy some of the formed elements and liberate their constituents into the plasma, it is possible to produce clotting by the simple addition of calcium salts.

HIRUDIN PLASMA. The action of hirudin is that of an antithrombin. It apparently combines with and neutralises thrombin. Hirudin plasma can therefore be made to clot by the addition of thrombin in sufficiently large quantities to combine with all the hirudin present and leave an excess over in the fluid.

PEPTONE PLASMA. If blood be received into peptone blood, obtained by the injection of large doses of peptone into the veins of another animal, the mixture does not clot, showing that peptone blood contains some substance which inhibits the processes of coagulation. This 'anticoagulin' must be produced by the organism itself as a result of the injection of peptone, and evidence has been brought forward by Delezenne and others that the seat of formation of the anticoagulin is in the liver. Whether the anti-substance partakes of the characters of an anti-thrombin has not yet been definitely ascertained. Peptone plasma can be made to clot by the addition of tissue extracts even in small quantities. It still contains all the fibrin factors, since it will clot on simple dilution or on the passage of a current of carbon dioxide. It needs the addition of large quantities of thrombin to bring about coagulation however.

THE TRANSUDATIONS. The earlier work on the mechanism of coagulation was largely carried out on the fluids obtained from the pericardial or pleural cavities, or on hydrocele fluid from the *tunica vaginalis*. These as a rule can be kept indefinitely without clotting, but will clot readily on addition of a few drops of blood, or the washings of a blood clot, or

* According to Rettger this statement is incorrect.

thrombin. They will not clot on the addition of tissue extracts. Though they contain leucocytes and even some red corpuscles, they are free from blood platelets. Their behaviour is readily explained by the assumption that they contain fibrinogen, but are free from thromboplastic material or prothrombin. In order to produce coagulation it is therefore necessary to add both these factors, as happens when we add blood, or to treat them with fully formed thrombin.

THEORIES OF COAGULATION. The incompleteness of our knowledge of what really happens in clotting is reflected in the great variety of theories which have been advanced to explain it. Any theory should have regard to the following facts: (1) Plasma contains all the substances necessary for clotting. (2) Blood does not clot in normal blood vessels. (3) Coagulation is a phenomenon closely related to the properties of the colloids concerned in it. (4) Essential factors in clotting are primarily fibrinogen and thrombin; secondary factors which govern the formation of thrombin are prothrombin, calcium salts and thromboplastic material. Thus far, though with different nomenclatures, most workers are now agreed. We can only mention the outlines of some of the theories.

Morawitz called the thromboplastic factor thrombokinasin, and considered that this substance, liberated by platelets or damaged tissues, in presence of calcium salts, converted a precursor, thrombogen in the plasma, into thrombin.

According to Nolf the essential factors in the production of blood clotting are three proteins: fibrinogen, thrombogen and thrombozym. The two former are produced in the liver, while the thrombozym is formed from the leucocytes. The clotting depends on a mutual interaction and precipitation of colloids with, as a result, either fibrin or thrombin. Thrombin differs from fibrin merely in containing less fibrinogen. For this reaction to take place, the presence of calcium is necessary as well as certain thromboplastic substances which act as centres of precipitation. Thrombin, according to him, is merely an unsaturated compound which is capable of taking up or uniting with more fibrinogen to form fibrin. He compares these actions occurring in the blood to the actions of digestive enzymes on proteins; fibrinogen is first precipitated as fibrin by union with thrombozym and thrombogen. This fibrin is then hydrolysed and dissolved by the further action of the thrombozym, which he regards as essentially proteolytic in character. That the whole blood does not coagulate within the vessels he explains by assuming that the cells of the blood and tissues are covered normally with an ultra-microscopic layer of fibrin which has no thromboplastic effect upon the plasma.

Howell's theory assumes that the thromboplastic material (cephalin) liberated by platelets or by other damaged tissue cells neutralises heparin, which normally maintains the fluidity of the blood *in vivo*, so that calcium salts can then convert prothrombin to thrombin. The fibrin is thrown down in needle-shaped crystals, and subsequently there is gelation of the whole plasma.

More recent views by Mills and by J. W. Pickering regard the various plasma colloids as forming a complex by physico-chemical union, instead of being mere mixtures of the various products such as can be artificially separated from the plasma. Under the conditions which obtain in the vessels the equilibrium of this complex is stable, but when the blood is shed various factors disturb this delicate balance.

According to Pickering the essential factors in determining the fluidity and clotting of the blood are:—(1) A fibrinogen-prothrombin complex; (2) a protective colloid; and (3) salts of calcium. During fluidity, the protective colloid preserves the fibrinogen-prothrombin complex from change. The absence of the coagulant action of thrombin *in vivo* is thus accounted for without postulating any anti-bodies. The coagulant action of thrombin on shed blood is equally intelligible, as surface changes, consequent on shedding, have disunited the protective colloid from the fibrinogen on which thrombin acts. The next step in clotting is the conversion of prothrombin into thrombin by ionised calcium salts and by other agencies, such as the detritus of cells and tissues. The thrombin thus formed converts fibrinogen into fibrin.

THE QUANTITY AND COMPOSITION OF THE BLOOD IN MAN

THE TOTAL BLOOD VOLUME. The amount of blood contained in the body can be estimated by Welcker's method. It is not sufficient simply to open one

of the blood vessels and allow the animal to bleed to death, because it is not possible in this way to obtain the whole of the blood present in the body. A small sample of blood is therefore taken from a blood vessel and diluted 100 times with distilled water to serve as a standard of comparison. The animal is then bled from a cannula placed in a large artery, while at the same time normal salt solution is led into a vein so as to maintain the vascular system as full as possible and allow of its being washed out by the action of the heart. When the heart ceases to beat, the blood vessels are thoroughly washed out by a stream of normal salt solution from the aorta. The animal is then minced up thoroughly and extracted with distilled water, so as to dissolve out the hæmoglobin still adherent to the tissues. These washings are filtered and mixed with the whole diluted blood, and the strength of the mixture in hæmoglobin is compared with that of the standard solution. In this way it is possible to estimate the total hæmoglobin present in the body in terms of the sample and so find the total amount of circulating fluid. It has been

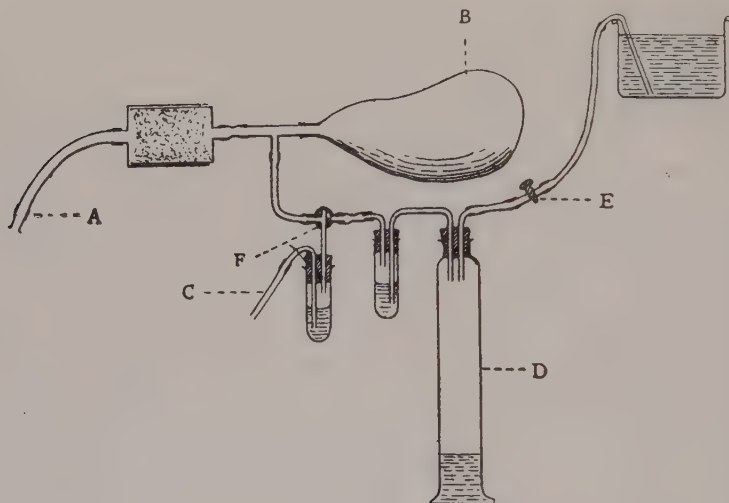


FIG. 340. Haldane's CO Method for Determining Total Blood Volume in Man.

found that the dog contains about 7·7 per cent. of his body weight as circulating blood, and the fraction of one-thirteenth has been taken as applicable to man on the basis of two observations made long ago on executed criminals.

According to Haldane, the average amount of blood in man is only about 4·9 per cent. of the body weight, *i.e.* about one-twentieth; in some cases, as in fat individuals, it may be as little as one-thirtieth. Haldane's method depends on the fact that carbon monoxide gas when inhaled combines with hæmoglobin, expelling the oxygen from the oxyhæmoglobin. If we allow a man to breathe a known volume of carbon monoxide until it is entirely absorbed, and then find that one-fifth of the hæmoglobin in his blood is saturated with carbon monoxide, we know that the whole blood could take up five times the bulk of carbon monoxide which the man has inspired. In this way we determine the total 'carbon monoxide capacity' of the blood, and since CO-hæmoglobin contains the same volume of carbon monoxide as oxyhæmoglobin does of oxygen, the same figure gives us the total 'oxygen capacity.' The total oxygen capacity enables us to determine the total amount of hæmoglobin in the body, and if we know the

percentage oxygen capacity of the blood it is easy to calculate the total volume of circulating fluid.

Before the carbon monoxide is administered, the percentage oxygen capacity, *i.e.* the volume of oxygen capable of being taken up by the hæmoglobin of 100 c.c. of the blood, is determined on a small sample of the subject's blood, either by the ferri cyanide method (p. 687) or by the hæmoglobinometer (p. 687). The subject is now made to breathe through a mouthpiece A (Fig. 340) into a bladder B of about 2 litres capacity. The carbon dioxide produced during the experiment is absorbed in the soda-lime vessel between the mouthpiece and the bladder. The oxygen as it is used up is replaced from an oxygen cylinder through the tube C. D is a graduated vessel containing pure carbon monoxide. While the subject is breathing in and out of the bag, a given volume of carbon monoxide is admitted into the bag, being driven out from the tube D by allowing water to flow through the tap E. The required volume of carbon monoxide is gradually driven in from the measuring cylinder at the rate of about 30 c.c. every two minutes. When the required quantity has been driven forward by the oxygen, an interval of two or three minutes is allowed to elapse. After this, a drop of blood is taken for analysis. It contains a certain amount of CO-hæmoglobin. The relative saturation of the blood in carbon monoxide is determined either by a colorimetric method or more simply by the use of Hartridge's reversion spectroscope.

The error is probably not greater than 10 per cent., which is negligible in comparison with the large changes in total blood volume which have been found to occur in certain cases of disease. The total record of two such observations by Haldane and Lorrain Smith may be here quoted :

NORMAL INDIVIDUAL

Body Weight in kilogrammes.	Volume of dry CO. absorbed in c.c. at 0° C.	Percentage saturation of Hb with CO.	Dry oxygen capacity of blood in c.c.
72.9	116	18.9	614
89.0	116	22.7	511

Oxygen capacity per 100 c.c. of blood in c.c.	Total amount of blood in grammes.	Grammes of blood per 100 grm. of body weight.	C.c. of oxygen per 100 grm. of body weight.
18.7	3455	4.75	0.84
18.2	2970	3.34	0.57

In applying this method in cases of disease, it is important not to give too large a dose of carbon monoxide gas. In a normal individual 30 per cent. of the hæmoglobin may be combined with carbon monoxide before any oxygen hunger is felt, and it is possible to saturate half the hæmoglobin with this gas, though with considerable discomfort to the individual. In cases such as heart disease, where the patient is at the very margin of his resources, even 30 per cent. diminution of the oxygen capacity of the blood may have serious results, and the carbon monoxide inspired must therefore be kept at the lowest limit at which it is possible to carry out a reliable determination of the relative carbon monoxide saturation of the blood sample.

A simpler but less accurate method of determining the total blood volume has been worked out by Keith, Rowntree and Geraghty. The method consists in injecting a non-toxic, non-diffusible dye substance into the blood stream and estimating its dilution. The dye used is 'vital red,' a chemical compound belonging to the triphenyl-methane series. In performing the test 6 to 8 c.c. of blood are removed from an elbow vein. From 10 to 18 c.c. of a 1.5 per cent. solution of the dye in distilled water is then slowly injected by the same needle. Five minutes later a second specimen of blood is withdrawn into a third syringe containing sodium oxalate to prevent the blood from clotting. A part of this sample is drawn into a hæmatocrit tube and centrifuged for twenty minutes at a high speed in order to determine the relative volume of corpuscles and plasma. The rest of both samples of blood are centrifuged in order to

obtain the plasma. These samples of plasma are then compared by preparing the following mixtures :

Standard	{ 1 part of the diluted dye solution. 1 part of the plasma before dye injection. 2 parts 0·8 per cent. NaCl solution.
Test	{ 1 part of plasma after dye injection. 3 parts 0·8 per cent. NaCl solution.

The two solutions are compared in a colorimeter and the test solution read off as a percentage of the standard. The following formula will give us the plasma volume :

If R be the percentage reading of test solution.

$$\frac{200}{R} \times \text{c.c. dye injected} \times 100 = \text{c.c. plasma.}$$

The blood volume is calculated from the hæmatocrit reading.

$$\text{Total blood volume} = \frac{100 \times \text{c.c. plasma}}{\text{percentage plasma in blood.}}$$

The total blood volume certainly varies appreciably with alterations in the condition of the animal, and may be found different on two succeeding days. It is influenced by posture, and by the height of the blood pressure as well as by the oxygen tension in the air breathed, and therefore alters with the altitude. Some of these variations we shall have to consider more fully in a later section. Any lowering of blood pressure causes an absorption of fluid from the tissues into the blood, so that the latter becomes more dilute.



FIG. 341.—Hæmatocrite. (From ANREP and HARRIS' "Practical Physiology.")

The blood content during the last stages of bleeding may contain little more than 50 or 60 per cent. of the hæmogoblin which was present in the first samples of blood, pointing to a corresponding dilution of the blood during these few minutes by means of tissue lymph. By this means, *i.e.* the absorption of fluid from tissues, the volume of circulating blood after a limited hæmorrhage is rapidly brought up to normal, so that there is a circulation of a fluid impoverished in corpuscles. The latter are made up in the course of a few weeks as a result of increased activity in the bone-marrow.

DETERMINATION OF THE RELATIVE VOLUMES OF CORPUSCLES AND PLASMA.

The relative volumes of corpuscles and plasma in any sample of blood may readily be determined by means of the *hæmatocrite*. This is a graduated capillary tube of uniform bore in which the specimen of blood, treated with a suitable anti-coagulant, is centrifuged at a high speed until the sedimented corpuscular layer shows no further shrinkage, and appears translucent. The depths of the layers of corpuscles and plasma are then read off, and are expressed as percentages of the whole length of the column of blood taken. It is usually found that in normal human blood the corpuscles occupy about 40 to 50 per cent. of the volume of the blood. In the horse the volume of corpuscles is about 55 per cent., in the dog 35 per cent.

CELL COUNT AND HÆMOGLOBIN CONTENT. In order to enumerate the red corpuscles, the blood is diluted with a known amount of an isotonic fluid and the number is counted in a measured volume of the mixture. The average number of red corpuscles is about 5,400,000 per cubic millimetre in healthy adult men and rather fewer, and more variable, in adult women. The enumeration of corpuscles is subject to considerable errors, usually not less than 10 per cent. Moreover, different conditions of the circulation

may cause variations in the relative distribution of plasma and corpuscles respectively in different parts of the circulation, so that the blood-count of a specimen from the capillaries of the finger or lobe of the ear may differ considerably from a similar count of the corpuscles in blood obtained directly from a minute vein or artery.

More important, therefore, is the determination of the hæmoglobin. For this purpose, a measured quantity of the blood, 2 to 20 c.mm., is obtained in a capillary pipette and mixed with a given volume of water. The red fluid thus obtained is compared with a standard. This latter in von Fleischl's instrument is a prism of coloured glass. The most accurate method is that due to Hoppe-Seyler, and Haldane, namely, the conversion of the blood sample into CO-hæmoglobin and its comparison with a standard specimen of CO-hæmoglobin, which is stable in solution and can therefore be kept in a sealed glass vessel for any length of time. The standard normal hæmoglobin in human blood is one with an oxygen capacity of 18.5 volumes per cent.

THE OXYGEN CAPACITY OF THE BLOOD. Instead of determining the hæmoglobin, we may measure directly the oxygen capacity of the blood, since the oxygen-binding power of this fluid is entirely dependent on the amount of hæmoglobin it contains. For this purpose we may make use of the fact discovered by Haldane, that the combined oxygen in oxyhæmoglobin is liberated rapidly and completely on addition of a solution of potassium ferricyanide to alkaline laked blood, and may thus be easily measured with the help of an apparatus similar to that used for determining urea in urine by the hypobromite method.

For smaller amounts of blood, such as can conveniently be drawn from man, the small blood-gas apparatus of Haldane is convenient (Fig. 342).

Into the flask B is placed 2 c.c. of 1 per cent. sodium carbonate solution and a few milligrams of saponin. The blood, (2 c.c.), rendered incoagulable with oxalate, is run into it, and well mixed, laked, and oxygenated by rotating in the flask for a few minutes. Then 0.25 c.c. of saturated ferricyanide solution is put into the small tube C, and the cork inserted, the control flask A being similarly corked, and both flasks placed under water in the bath D, the three-way taps J and K being open to the air with the T bore thus : T. After allowing a few minutes to attain temperature equilibrium, the levelling tubes H and I (filled with water containing a little saponin or bile-salts) are adjusted so as to bring the water in F and G to the mark, and the taps J and K are then turned with the bore thus : $\neg$. The burette E is then read, the flask B is tilted so that the ferricyanide runs into the blood solution, and the flask is shaken in the bath until no more gas is evolved. After allowing a few minutes to equalise any differences of temperature, the water level is again adjusted in F and G, and the volume of gas evolved read off on the burette E, and reduced to dry volume at N.T.P. (For Barcroft's apparatus see p. 854.)

THE SPECIFIC GRAVITY OF THE BLOOD. The specific gravity of the blood may be determined by collecting blood in a capillary tube and discharging drops of it into a liquid of known specific gravity, with which it will not mix. Thus, we can use a mixture of chloroform and benzene and then add chloroform or benzene, as the case may be, until the drop neither rises nor falls. The specific gravity of the mixture is then taken. The specific gravity varies between 1055 and 1066, being lowest in women. It is increased by loss of water, as after profuse perspiration, or by passive congestion of the part from which the sample is taken. It is also increased as a result of any operation upon a serous cavity in consequence of exudation of plasma in the inflamed or irritated part. It is diminished as the result of bleeding. The specific gravity of serum is 1028 to 1032, of corpuscles about 1090. It is interesting to note that the specific gravity of the blood is highest in the fœtus at full term, when it amounts to 1066, contrasting with that of the mother at the same time, the specific gravity of whose blood is only 1050. The specific gravity rapidly falls after birth.

THE SUSPENSION STABILITY OF THE BLOOD. From the size of the red cells and the difference in specific gravity between them and the plasma, it can be calculated that when blood is allowed to stand the corpuscles should sink at a speed of about 0.2 mm.

per hour ; yet the experience of centuries has shown that the speed with which sedimentation occurs is far more rapid and shows enormous variations.

In the days when blood-letting was almost universal in the treatment of disease, it was a frequent observation that on allowing the blood to stand there was formed at the surface of the clot a pale layer, known as the *buffy coat*. It is evident that the buffy coat owes its production to the fact that the corpuscles have settled so rapidly that the clot is formed in part in the supernatant plasma, and is, therefore, pale in colour.

Fåhræus has studied the sedimentation of citrated blood by allowing samples to

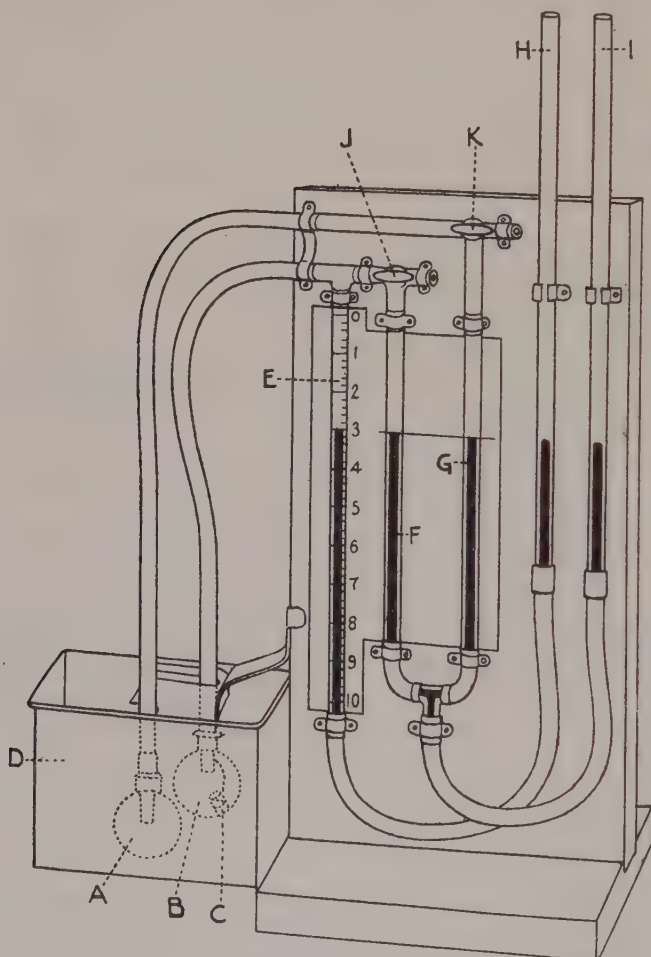


FIG. 342. Haldane's Blood-gas Apparatus.

stand undisturbed in long narrow tubes, and measuring the length of clear plasma after one hour. The following average results were obtained :—

New-born children	0.5 mm. per hour.
Normal men	3.3 " "
Non-pregnant women	7.4 " "
Pregnant women at term	44.9 " "

The increased rate of sedimentation is due to the phenomenon known as *agglutination*, which consists in the corpuscles aggregating together into clumps. In blood with a sedimentation value of 1 mm., each clump consists of about eleven corpuscles, while one with a value of 75 consists of clumps each composed of about 58,000 corpuscles. If

the corpuscles and plasmata be separated off from two bloods with very different suspension stabilities, *e.g.* normal male and gravid female bloods, and then exchanged, it is found that the speed of settling is determined by some constituent of the plasma and not of the corpuscles. This constituent is usually associated with the globulin fraction.

BLOOD GROUPS. The phenomenon of agglutination is often shown in an exaggerated form when the blood of one species is added to the blood, or to the plasma or serum, of another. If, for instance, a drop of human blood be mixed, on a slide or white plate, with some horse serum, the agglutination is so conspicuous that it is evident to the unaided eye. These facts acquire great practical importance, because agglutination is the precursor of hæmolytic, and because the plasma of one human being frequently causes agglutination of the corpuscles of another. In carrying out the urgent operation of blood transfusion, it is therefore a matter of great importance to ensure that the corpuscles of the donor will not be agglutinated by the plasma of the recipient. It is found that human beings fall into four groups, when agglutination tests are performed; these are shown in the following table. The + signifies agglutination.

		Serum			
		I.	II.	III.	IV.
Corpuscles.	I	—	+	+	+
	II	—	—	+	+
	III	—	+	—	+
	IV	—	—	—	—

The corpuscles of Group IV. are not agglutinated by the plasma of any group, and Group IV. are accordingly called 'Universal Donors,' since their blood is safe for transfusion into any person. In Group I. the plasma does not agglutinate any corpuscles, so that people belonging to this group could receive blood from any healthy person. The other groups are as shown. Thus Group III. could act as a donor to Groups I. or III. only.

It is usual to carry out grouping tests by the use of tested sera belonging to Groups II. and III. Drops of the blood of the person to be tested are mixed with a drop of each of these, and, as in the table :

Group I. is agglutinated by II. and III.
 Group II. " " III.
 Group III. " " II.
 Group IV. " " neither.

Among normal people, about 2 per cent. belong to Group I., 40 to Group II., 15 to Group III., and 43 to Group IV.

THE REACTION OF THE BLOOD. The blood is slightly alkaline to litmus. Like any other alkaline solution, it can be titrated with an acid. Such a procedure, however, gives a measure, not of the degree of alkalinity, but of the alkaline reserve—*i.e.* of the total amount of base in combination with weak acids which can be replaced by a stronger acid. This *alkaline reserve* consists almost exclusively of sodium bicarbonate.

In Van Slyke's method the alkaline reserve of the plasma is determined by finding out how much CO₂ is evolved from 1 c.c. of the oxalated plasma, when this is treated

with 0.5 c.c. of 5 per cent. sulphuric acid. Since the amount of carbon dioxide taken up depends on the partial pressure of the CO_2 in the atmosphere to which the plasma is exposed, the plasma is first shaken up with alveolar air provided by the experimenter himself, which always contains about 5.5 per cent. of CO_2 .

Normal human blood plasma treated in this way yields between 0.6 and 0.7 c.c. of CO_2 per cubic centimetre, which corresponds to about 0.2 per cent. of sodium bicarbonate.

The *hydrogen ion concentration* of the blood can be determined by the electrical method, or by the use of indicators which vary in their colour with change of reaction, as described on p. 89.

By these methods the hydrogen ion concentration of the blood, *i.e.* of the plasma, at 38° is found to be 0.4×10^{-7} , or pH 7.4. It might be thought that with such a feeble alkalinity the merest trace of acid added to the blood would suffice to make it acid. It is found, however, that a relatively large proportion of an acid must be added to the blood in order to produce a considerable change in its reaction. This is due to the fact that the sodium bicarbonate acts as a 'buffer'—*i.e.* a substance which can take up acid or alkali with a minimal change of reaction. As in other buffer systems (*v.* p. 87) the hydrogen ion concentration depends on the ratio of the weak acid to its salt, *i.e.* to $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$. This in blood is usually about $\frac{1}{20}$ when molar con-

centrations are taken. This property of the blood of retaining a nearly constant reaction, even though fixed acids are added to it, is of immense importance, since all cellular functions are acutely sensitive to changes in reaction, and as we shall see later, the activity of the respiratory centre is largely dependent on the hydrogen ion concentration of the blood with which it is bathed.

The alkaline reserve of the blood is significant, since pronounced diminution indicates in all probability the production of fixed acids in the tissues, and a progressive reduction will precede the point at which the 'buffer' action of the sodium bicarbonate is lost, and the blood then responds to any addition of acid by a considerable change in reaction. It is only when the alkaline reserve has been greatly reduced that a true condition of *acidæmia*, or increased H-ion concentration, can come into being.

THE OSMOTIC PRESSURE OF THE BLOOD. Since the blood serves as a circulating medium, by means of which the composition of the tissue juices is maintained constant, its osmotic pressure must be of considerable importance. The osmotic pressure of the blood depends on its molecular concentration and can be determined by any of the methods mentioned earlier (p. 80), *e.g.* by the determination of the freezing-point. The depression of freezing-point, Δ , of mammalian blood is about 0.56 and varies between 0.54 and 0.60. This is equal to that of a 0.9 per cent. sodium chloride solution, which is therefore taken as isotonic with the blood. Since the corpuscles are in osmotic equilibrium with the plasma, laking the blood does not alter its freezing-point or its osmotic pressure.

THE ELECTRICAL CONDUCTIVITY OF THE BLOOD. In a solution it is only the dissociated ions which have the power of carrying electric charges. The conductivity of blood serum is therefore determined almost entirely by its content in salts. Since this is approximately constant, the conductivity of serum varies within very narrow limits. The conductivity of blood varies, however, within wide limits. The corpuscles present a resistance to the passage of the charged ions and therefore of the electric current through them, so that the larger the number of corpuscles contained in a given specimen of blood the lower will be the conductivity of the latter. Stewart has made use of this fact as a basis for a method of determining the relative volume of corpuscles and plasma. Owing to the fact that the red cells carry a negative charge, they move towards the anode when an electric current is passed through the blood.

THE GENERAL COMPOSITION OF THE BLOOD

Human blood contains from rather over one-third to one-half of its weight of corpuscles. It contains from 20 to 25 per cent. of solids. Blood plasma is

resolved by clotting into serum and fibrin. The fibrin forms only 0.2 to 0.4 per cent. of the total weight of blood. The serum contains, in 100 parts, 8 to 9 parts of solids, of which 7 to 8 parts consist of proteins, while the salts make up about 1 part. The chief salt present in the serum is sodium chloride, and next to this comes sodium bicarbonate, and besides these two we find traces of potassium, sodium and calcium chlorides, and phosphates. Traces of fats, cholesterol, lecithin, glucose, urea, amino-acids and other nitrogenous extractives are constantly found in the serum. The fats are much increased after a meal rich in them and may give the serum a milky appearance. The red corpuscles contain from 30 to 40 per cent. total solids. Of the solid constituents, hæmoglobin forms nine-tenths; the other tenth corresponds to the stroma, consisting of stroma protein (nucleo-protein), lecithin, cholesterol and salts. There is a striking contrast between the salts of the corpuscles and those in the serum, the former consisting chiefly of potassium phosphate, the latter of sodium chloride, which in some animals is entirely wanting in the corpuscles.

The following table shows the average percentage composition of human blood:—

NORMAL HUMAN BLOOD

	Per cent. in Whole Blood.	Per cent. in Plasma.	Per cent. in Corpuscles.
Total solids	21.0	9.9	32.0
Inorganic solids	0.75	0.8	0.7
Serum albumin	2.8	5.6	—
Serum globulin	0.95	1.9	—
Fibrinogen	0.25	0.4	—
Hæmoglobin	14.5	0.0	29.0
Non-protein nitrogen	0.03	—	—
Urea nitrogen	0.012	—	—
(= urea)	0.026)	—	—
Amino nitrogen	0.006	—	—
Creatinine	0.001	—	—
Creatine	0.005	—	—
Uric acid	0.002	—	—
'Total fat'	—	0.65	—
'Lecithin'	0.3	0.2	0.4
Cholesterol	0.15	0.15	0.15
Total acetone bodies (as acetone)	0.001	—	—
Sodium	0.20	0.335	0.065
Potassium	0.20	0.02	0.38
Calcium	0.007	0.01	0.004
Magnesium	0.003	0.0025	0.0035
Iron	0.05	0.00	0.10
Chlorine (chloride)	0.29	0.36	0.20
Phosphorus, inorganic	—	0.0035	0.15
„ 'lipoid'	—	0.0075	—
„ organic	0.053	—	—
Sulphate sulphur	0.0005	—	—
Bicarbonate (as HCO_3)	—	0.15	—
„ (as NaHCO_3)	—	0.21	—

THE PROTEINS OF THE PLASMA. The plasma is generally described as containing a number of different proteins belonging to the class of coagulable proteins. No albumoses or peptones are present. Since the plasma in

clotting gives rise to fibrin and serum, we may divide its protein constituents into those which are the precursors of fibrin and those which are still contained in the serum.

The Precursors of Fibrin. Fibrinogen is a globulin occurring in the plasma and converted on coagulation into fibrin. This, and the other precursors of fibrin, those involved in the production of thrombin, have already been dealt with.

Fibrin. Fibrin is easily obtained by whipping blood as it flows from the vessels with a bundle of wires or twigs, and then washing the stringy threads so obtained under a stream of water. As prepared in this way it always contains fragments of leucocytes, blood platelets and stromata, which have become entangled in its meshes. In order to prepare fibrin in a pure state, it is necessary to get it by the action of thrombin on a pure solution of fibrinogen. Fibrin is insoluble in water and in dilute salt solutions. It slowly dissolves in 5 per cent. sodium chloride, but is converted in this process into soluble globulins. It is probable that its solution is effected by the agency of minute traces of proteolytic enzymes adherent to the fibrin as it is precipitated. This probability is strengthened by the fact that a certain amount of albumoses is always found in the fluid along with the soluble globulins. In dilute acid, such as 0.2 per cent. hydrochloric acid, fibrin swells into a clear jelly which very slowly undergoes solution with the formation of acid albumin and proteoses.

THE PROTEINS OF THE SERUM. The serum proteins are generally grouped in two classes: the serum albumins and the serum globulins. All the proteins are completely precipitated by saturation with ammonium sulphate. By half-saturation with this salt only the globulins are precipitated and can be separated from the serum albumins by filtration. The proportion of globulin to albumin as determined in this way is known as the 'protein quotient.' It can be most readily determined from observation of refractive index and viscosity. It varies in different animals, but in the same individual it is almost constant in the blood, serum, lymph and serous transudations, though the total amounts of protein in these may be very different.

Serum Albumin. Serum albumin remains in the serum after half-saturation with ammonium sulphate. It can be precipitated from this by complete saturation with ammonium sulphate. Serum albumin is soluble in distilled water. Its solutions, therefore, can be dialysed indefinitely without any precipitation taking place.

The Globulins. The globulins of serum, known as *serum globulin*, are obtained by half-saturation with ammonium sulphate. Their solutions in salt coagulate at about 75° C. Since globulin is insoluble in distilled water, it is precipitated on dialysing serum against distilled water. The precipitate obtained in this way is not, however, so great in amount as that obtained on half-saturation, and on this account the globulin fraction of the serum proteins has been divided into two fractions, namely, *euglobulin*, precipitable by dialysis, and *pseudo-globulin*, not precipitable by dialysis, but thrown down on half-saturation with ammonium sulphate. Pseudo-globulin is, however, not soluble in complete absence of salts, and is therefore thrown down by electro-dialysis, which removes the last traces of salt more efficiently than does ordinary dialysis.

A thorough study of serum globulin by Hardy has shown that this body forms combinations with acids, alkalies, or neutral salts. With acids and alkalies the globulin forms 'salts' which ionise in solution so that in an electric field the entire mass of protein moves. These salts cannot be precipitated by dialysis. In them the globulin acts much more strongly as an acid than as a base, so that a weak acid, such as acetic acid, has a much smaller dissolving power for globulin than has the equivalent amount of hydrochloric acid, and boric acid has a very slight power indeed. Owing to the much stronger acid character of globulin it is found that weak ammonia dissolves it almost as well as strong alkalies. With neutral salts, globulins form molecular com-

pounds which are stable only in the presence of a comparatively large excess of salt. In all its solutions globulin is present in large molecular aggregates, so that it is impossible to filter a globulin solution through a porous clay cell.

THE CONDITION OF THE PROTEINS IN THE BLOOD SERUM. Although it is easy by such simple means as the addition or removal of neutral salts to separate one or more different forms of protein from serum, we have evidence that these proteins do not exist side by side in the serum, but are combined to form what we may term *serum protein*, which acts as a whole and differs in its qualities from many of those of its constituent globulins or albumins.

When a current is passed through blood serum no movement of protein takes place (Hardy). Alkali globulin therefore cannot be present. Salt globulin might be assumed to be present since it does not ionise in solution, but serum is not precipitated by simple addition of acid, which would readily precipitate salt globulin in alkaline solution. Moreover, serum can be readily filtered through a porous cell, and this method is adopted for obtaining it free from contamination by micro-organisms; yet globulin in any of its solutions will not pass through a porous cell. If globulin be present as such in the serum, it is therefore not ionised, but the agent which dissolves it must be something more than alkali or salt, since either alone or together they will not produce a solution which will pass through a porous cell. Serum has still the power of taking up globulin and will dissolve almost its own volume of precipitated globulin, though in oxalate serum there is not a trace of alkali globulin nor of any ionised protein. We are justified, therefore, in concluding that serum protein may be regarded as a complex unit. By simple means, such as dialysis, dilution or addition of salt, this unit can be broken up with the separation of the various proteins which we have designated as serum albumin and serum globulin, &c. The question naturally suggests itself whether in plasma we have not a similar combination of all its varied colloidal constituents to form one labile mass of fluid protoplasm. The study of the phenomenon of coagulation certainly tends to support such a view.

THE CIRCULATION

CHAPTER XXXII

GENERAL FEATURES OF THE CIRCULATION

IN order that the nutrition of the tissues may be properly carried out, and that they may be able to free themselves of their waste products, the blood which flows through them must be continually renewed. For this purpose

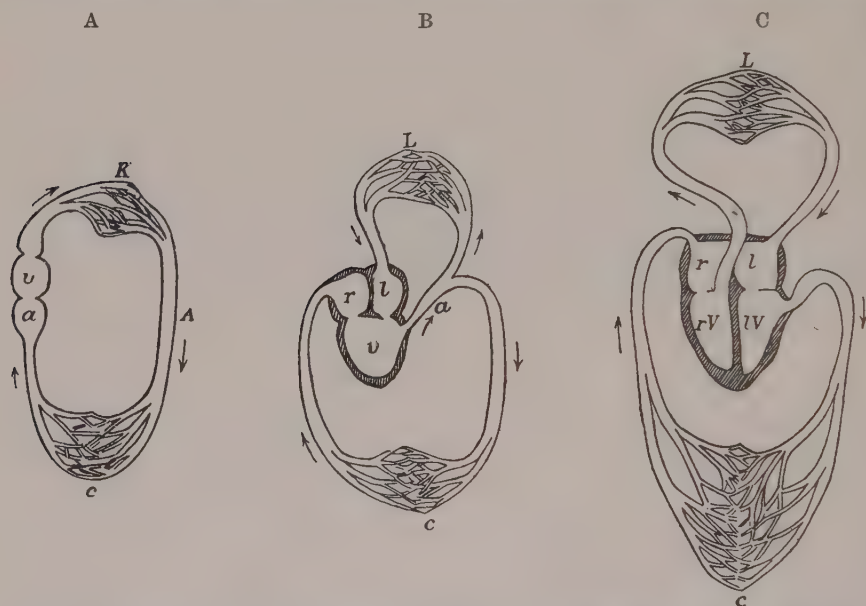


FIG. 343. Diagram of Circulatory System in A, Fish; B, Amphibian (Frog); C, Mammal.

v. Ventricle.

a. Auricle.

K. Gill capillaries.

A. Aorta.

c. Systemic capillaries.

L. Lung capillaries.

r, *l*. Right and left auricles.

rV, *lV*. Right and left ventricles.

every part of the body is supplied with tubes—blood vessels—of varying size and structure.

In the tissues the blood is passing continuously through a close mesh-work of capillaries, minute vessels with walls consisting of a single layer of delicate endothelial cells, which permit of a free interchange of material by diffusion between the blood within and the tissue fluid outside the vessel. The movement of the blood is maintained by the heart, the blood being brought from the heart to the tissues by the arteries, and carried back from the tissues to the heart by the veins.

In all the vertebrates the vascular system is closed, *i.e.* communicates at no point with the tissue spaces or coelomic cavity. It is found in its simplest form in fishes (Fig. 343, A), where the heart consists of one auricle and one ventricle. The blood is

received from the great veins into the auricle. The walls both of auricle and ventricle contract rhythmically. By the contraction of the auricle the blood is forced into the ventricle and this, when it contracts, sends the blood on into the bulbus arteriosus. From the bulbus the blood passes through the branchial arteries into the gills, where it takes up oxygen from the surrounding water, and then flows on into the aorta, by which it is distributed to the various organs of the body. From the capillaries of these organs the blood is collected by the veins and is carried once more back to the auricle. The fish heart is thus entirely on the venous side of the vascular system.

In amphibia, such as the frog, the heart consists of two auricles and one ventricle. The right auricle receives venous blood from the body by means of the *venæ cavæ* and forces it by its contraction into the ventricle. From the ventricle the blood passes into the aorta, whence it is carried partly by the pulmonary artery to the lungs, partly by arteries to the different organs of the body. The blood, which has passed through the lungs and been arterialisied, flows through the pulmonary veins to the left auricle, whence it passes into the ventricle and mixes with the venous blood which is arriving from the right auricle. The pulmonary circulation is thus merely a branch of the general or systemic circulation. The bulbus aortæ in the frog is divided into two parts by means of a spiral valve, by which a partial separation of the blood coming from the right and left auricles is effected, and the venous blood from the right auricle directed especially into the pulmonary artery.

In birds and mammals the heart has become entirely divided into two halves, right and left, which have no communication with one another except by way of the blood vessels and capillaries. The right auricle receives the venous blood from all parts of

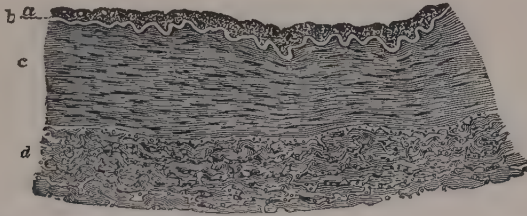


FIG. 344. Transverse Section of Part of the Wall of the Posterior Tibial Artery ($\times 75$). (SCHAFER.)

- | | |
|--|---------------------------------------|
| a. Endothelial and sub-endothelial layers of intima. | c. Media consisting of muscle fibres. |
| b. Lamina of elastic tissue. | d. Adventitia. |

the body and sends it on to the right ventricle, whence it is forced into the lungs along the pulmonary artery. In the lungs it takes up oxygen and becomes arterial and is returned by the pulmonary veins to the left auricle and so to the left ventricle. The rhythmic contractions of the left ventricle then force the blood into the aorta, whence by the branching arteries it is carried to all parts of the body.

The whole vascular system is distensible and elastic, so that its capacity will increase with the pressure of the blood contained in it. Since the driving force is furnished by the heart, the pressure which causes the flow of blood through the system must decline as we pass from the arterial to the venous side. The chief function of the large arteries is to serve as elastic conduits, whereas the small arteries or arterioles leading from the arteries to the capillaries have in addition the function of regulating the amount of blood flowing through the capillary area of the organs which they supply. The veins have the function of conducting blood at a low pressure from capillaries to heart and of storing up any excess of blood which is not immediately taken up by the heart.

Corresponding to this difference in function we find variations in the structure of the blood vessels according to their situation in the circuit. The vessels which carry the blood from the heart to the tissues, the arteries, are thick-walled, and contain an abundance of muscular and elastic elements in their walls. The typical medium-sized artery is described as consisting of three coats (Fig. 344): an *intima* lined by a continuous layer of flattened endothelial cells, which rest on a well-marked lamina of yellow

elastic tissue; a *media* composed of unstriated muscular fibres arranged mainly circularly; and an external coat or *adventitia* of fibrous tissue, with a number of longitudinal elastic fibres. Near the heart, in the great vessels such as the aorta and its larger branches, there is a preponderance of elastic tissue as compared to the muscular; and we find in the media alternate layers of muscle fibres and fenestrated elastic membranes. In the smallest arteries on the other hand, the arterioles, the elastic element entirely disappears, so that the wall consists of muscle fibres, chiefly circular, lined by the endothelium. In these vessels a contraction of their walls may result in an entire obliteration of the lumen, so shutting off altogether the supply of blood to the capillaries beyond. The capillaries, though formed merely of a single layer of endothelial cells, also possess the power of contracting and relaxing, and so admitting of a larger or smaller flow of blood to the tissues according to their local needs. In the veins the same three coats can be distinguished as in the typical artery, but the wall of the vessel is much thinner in proportion to the lumen. In the vein, moreover, there is a preponderance of the fibrous tissue elements, the muscular and elastic tissue being but little marked. On this account the vein collapses unless it is distended by some internal pressure.

The histological difference between veins and arteries is of importance for the understanding of the distribution of pressures in the vascular system, since the distensibility of these vessels is conditioned by their structure. In

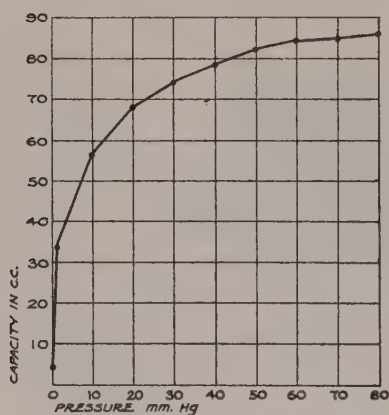


FIG. 345.

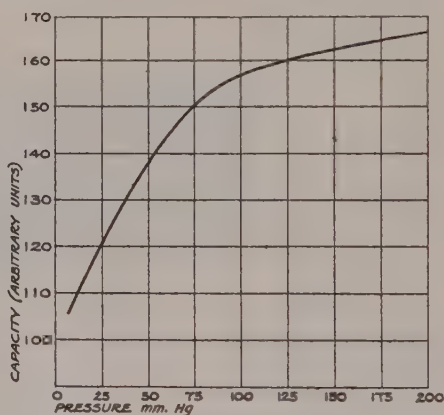


FIG. 346.

Fig. 345 is represented the distensibility, *i.e.* the increase in capacity of a vein under gradually increasing internal pressure. It will be seen that the capacity, which is negligible at zero pressure, becomes considerable on raising the pressure to 1 mm. Hg. A further rise of pressure to 10 mm. Hg causes a very large increase in volume, but from this point the increments of volume with rising pressure rapidly diminish. On the other hand, the artery, which has a certain capacity at zero pressure, increases its capacity much more slowly with rise of pressure, and the increment of capacity becomes gradually less as the internal pressure rises. In Fig. 346 is shown the distensibility of an artery to sudden alterations of pressure such as occur with each heart beat. It was found by Bramwell and Hill that in a normal carotid artery, whereas at a pressure of 50 mm. Hg a rise of 2 mm. Hg was sufficient to increase the capacity 1 per cent., at 80 mm. Hg a rise of 5 mm. was required, at 110 mm. Hg 10 mm., at 150, 20 mm. Hg, and at 200 mm. Hg as much as 28 mm. Hg increment was necessary. This means that the arterial wall becomes more rigid with increasing distension.

As the arteries branch, although each branch is smaller than the parent vessel, the total area of the two branches into which the vessel divides is greater. Thus there is a continual increase in the cross area of the bed

of the blood stream as we pass from the heart towards the periphery. This increase is especially marked at the junction between the capillaries and the arterioles on one side and the venules on the other, so that the total area of the bed in the region of the capillaries can be taken as about 800 times that of the area of the aorta where the blood leaves the heart.

This figure would apply only to normal conditions, under which but a portion of the capillaries are open and pervious to the blood current. By the opening up of previously closed capillaries, the capacity of the capillaries in active muscle may be increased to many times that of these vessels in a resting muscle. In fact, a general and simultaneous dilatation of all the capillaries of the body may increase the capacity of the stream bed to such an extent that there is an insufficient return of the blood to the heart, and a condition of 'surgical shock' is brought about.

DISCOVERY OF THE CIRCULATION. The discovery that the blood travels round in a circuit, returning again and again to the same point, was made by William Harvey, physician to Charles I., and was given to the world in a book of seventy-two pages, printed at Frankfurt in 1628.

This, the greatest discovery in the whole of medical science, of which indeed it laid the foundation, was the result of prolonged experiment and patient observation, but in his masterly though modest treatise Harvey shows that the circulation is a logical necessity to which we must be led by the contemplation of certain elementary facts.

(1) The arrangement of the valves in the heart and veins is such as to allow of a movement in one direction only.

(2) 'If the heart is grasped in the hand, it may be felt to become harder during its action.' When this happens, the ventricles become smaller and the arteries expand; if an artery is severed, blood spurts from its central end at each heart contraction.

(3) Since, at each contraction of the heart blood is forced into the arteries and cannot return, it follows that, even if only a small quantity were so expelled, there would not be enough blood in the heart, or even in the whole body, for the process to continue, nor could all this blood remain in the arteries. The heart must, therefore, receive blood continuously from the veins and pass it out continuously into the arteries. If a vein is compressed or tied by a ligature, it swells up on the side furthest from the heart, and collapses on the side nearest the heart. With an artery it is the reverse. Hence the blood must be passing continuously from the arteries, through the tissues into the veins. Similarly, the blood in the right ventricle must pass by way of the pulmonary artery and lungs to the pulmonary veins and so reach the left side of the heart.

Harvey could not be certain how the blood passed through the tissues from arteries to veins, but with the use of the microscope, the capillaries were discovered by Malpighi in 1661, and the missing link in the argument was thus provided.

THE CIRCULATION

CHAPTER XXXIII

PHYSIOLOGY OF THE HEART

THE CAUSATION OF THE HEART BEAT

IF the heart be cut out of the body of a cold-blooded animal, such as the frog or tortoise, it will continue to beat with the normal sequence of its different chambers for hours, or even days, provided that it be kept cool and moist. In the case of a warm-blooded animal, the heart is similarly capable of continuing its rhythmic contractions for some little time after excision. The fact that in both cases the heart will continue to beat after removal from the body, shows that the causation of the heart beat is to be sought in the walls of the heart itself. The heart wall consists of a muscular tissue resembling in many respects voluntary muscle; like this, it presents longitudinal and transverse striations; like this, it is capable of contracting in response

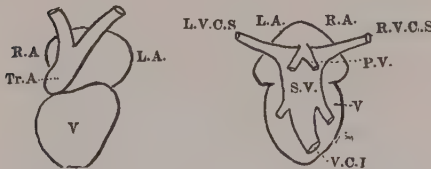


FIG. 347. Diagram of Frog's Heart. (After CYON.)

v, ventricle; R.A., L.A., right and left auricles (atria); S.V., sinus venosus; P.V., pulmonary veins; L.V.C.S. and R.V.C.S., left and right superior vena cava; V.C.I., vena cava inferior; Tr.A., bulbus arteriosus.

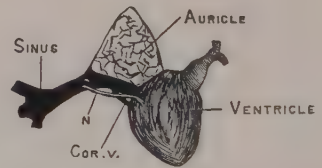


FIG. 348. Tortoise's Heart (after GASKELL) as it appears when Suspended for Registering the Auricular and Ventricular Contractions. N, nerve trunk with fibres connecting Remak's and Bidder's ganglia; COR. V., coronary vein.

to direct stimulation. The histological unit is a muscle cell, roughly quadrilateral when viewed from the surface. Each cell has a nucleus near its centre, and is joined to adjacent cells to form fibres. No sarcolemma is present, and the fibres lying side by side are connected at frequent intervals by short bridges. The contractile units are thus not separate, as in voluntary muscle, but are in protoplasmic and functional continuity.

ANATOMY OF THE HEART IN THE FROG AND TORTOISE. The hearts of the frog and of the tortoise have figured largely in the researches on the causation of the heart beat.

The frog's heart (Fig. 347) consists of the sinus venosus which receives the anterior and posterior venæ cavæ, two auricles, one ventricle, and the bulbus arteriosus which opens into the two aortæ. The venous blood from the body flows into the sinus venosus by the three venæ cavæ, and thence into the right auricle, while the left auricle receives

the blood from the lungs. The ventricle thus receives mixed arterial and venous blood, the arterial blood being directed by the spiral valve of the bulbus aortæ so as to flow chiefly towards the head.

The muscular fibres of the frog's heart are less highly developed than those of the mammalian heart. They are spindle-shaped, and only dimly cross-striated. The cross-striation becomes more distinctly marked as we proceed from sinus to ventricle, the sinus muscle fibre representing the most primitive condition. There is complete muscular continuity between all the cavities of the heart. The circular ring of muscle at the junction of sinus with auricles and of auricles with ventricle presents only slight traces of cross-striation.

The heart is well supplied with nerve fibres and ganglion cells. The two vagi enter the sinus venosus and branch just under the pericardium. Here they become connected with a collection of nerve cells, known as Remak's ganglion. From the sinus the two vagi, now called septal nerves, pass down in the interauricular septum, one in front and the other behind. Near the auriculo-ventricular groove they enter two collections of ganglion cells, called Bidder's ganglia. From these ganglia non-medullated fibres are distributed to surrounding parts of the auricle and to the whole of the ventricle. In the upper third of the ventricle occur scattered ganglion cells attached to the nerve fibres. These are quite absent in the lower half or two-thirds.

In the tortoise (Fig. 348) the two auricles are bound together by a flat band of tissue, which serves also to connect the sinus with the ventricle. The septum between the auricles arises from the central line of this junction wall. The two vagus nerves pass into a large accumulation of ganglion cells in the sinus, and thence along the basal wall to the auriculo-ventricular groove, lying just under the pericardium. In the groove they pass into a collection of ganglion cells, whence fibres are given off to both auricles and ventricle. As they leave the sinus, a branch of the right nerve runs along the coronary vein, which conveys blood from the ventricular wall to the sinus. Thus the nerves of the tortoise's heart are altogether more accessible than those of the frog's heart. In other points the tortoise's heart is similar to the frog's heart.

THE CONTRACTION OF THE COLD-BLOODED HEART

The frog's heart, when intact, beats regularly, the contraction starting in the sinus, then travelling to auricles, ventricle and bulbus. If, however, the heart be removed by cutting it across the sino-auricular junction, or if the auricles be functionally separated from the sinus by a ligature round this junction (Stannius ligature), the auricles and ventricle stop in an uncontracted condition (diastole), while the sinus goes on beating regularly. After the lapse of a period varying from five minutes to half an hour, the detached part of the heart begins to beat, at first slowly and then more rapidly, but never attaining the rate of the sinus. The auricles beat first and then the ventricle. If now the ventricle be cut away by an incision in the auriculo-ventricular groove from the auricles, the latter go on beating; while the former, after a few beats due to the excitation of the incision, stops beating, and only after a considerable time may begin again to contract very slowly. On the other hand, the lower two-thirds of the ventricle, if separated functionally from the rest of the heart by a ligature, or by section, never beats again, under normal circumstances. To single stimuli it responds with a single beat, not with a series of beats as the whole heart does. It can be made to beat rhythmically, however, by raising the pressure within its cavity.

There is thus a descending scale of automatic power in the different parts of the frog's heart—from the sinus, where it is highest, to the lower parts of the ventricle, where it is very slight. The normal sequence of events—*i.e.* the subordination of the ventricle to auricles, and auricles to sinus, so that the beat always follows in the order, sinus, auricles, ventricle, bulbus—can be ascribed to the difference between the natural rhythms of these different cavities. It is possible to record the contractions of each of these parts of the heart separately, after having divided them, either functionally by crushing the intervening tissue, or by actual

section. Under such conditions it is found that there is a descending scale of rhythm from sinus to bulbus, the contractions of the sinus being most frequent, those of the ventricle and bulbus the least frequent. Thus it is impossible for the ventricle to function at its own rhythm, since before it is ready to beat again spontaneously after performing one contraction, it receives an impulse from the auricles which induces a beat. That the normal sequence of contractions is dependent on the domination by the sinus, is shown by the fact that, by exciting the ventricle by means of induction shocks repeated at a rhythm slightly quicker than that of the sinus, it is possible to induce a reverse rhythm, the order of the beat being now ventricle, auricles, sinus venosus. It is clear, therefore, that the portion of the heart which beats most rapidly, dominates the rest.

The normal dependence of the ventricular rhythm on the beat of the sinus may be shown by a simple experiment. The ventricle is connected with a lever suspended by a

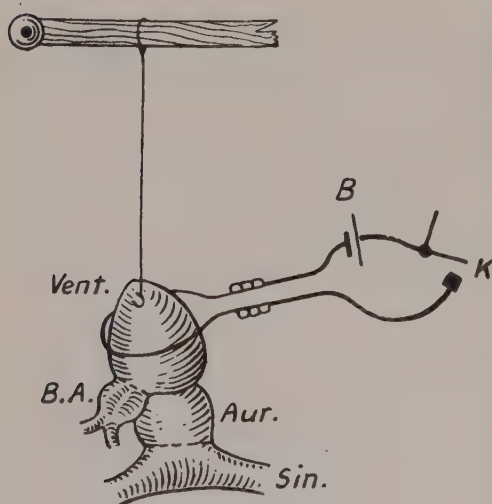


FIG. 349.

spring so as to record its contractions on a drum. A platinum loop connected with a galvanic battery is put round the heart, either round the sinus or round the ventricle (Fig. 349). When a current is allowed to pass through the wire loop, the corresponding part of the heart is warmed. When the ventricle alone is warmed, the beats become larger, but the rhythm is unaltered. On lowering the loop so as to warm the sinus, the rhythm of the whole heart is quickened, but the size of the ventricular beats is unaffected.

The different rhythmic power of these parts of the heart is apparently connected with the histological characters of the muscle fibres at each part. The lowly differentiated sinus cell has well-marked rhythmic power and a quick rhythm of beat, but is not able to exert much force in its contraction. The more highly differentiated ventricle cell has only a slight rhythmic power, but beats forcibly and is a good servant of the sinus.

NEUROGENIC THEORY OF HEART BEAT. It was formerly thought that the ganglia (Remak's and Bidder's ganglia) were responsible for the initiation of the beats and for the co-ordination of the different cavities. This theory has been abandoned since it was shown by Gaskell and by Engelmann that—

- These ganglia may be excised in the frog and tortoise without altering the automatic contractions or normal sequence of beat.
- Remak's ganglia are merely distributing ganglia for the vagus nerves to the heart. They may be paralysed by nicotine without disturbing the beat.
- A small portion of cardiac muscle, entirely free from ganglion cells, may be seen to contract rhythmically.
- The heart in the developing chick begins to contract at a date prior to the growth into it of nerve cells.

Finally it has been shown more recently that isolated cardiac muscle cells, cultivated outside the body, show rhythmic contractions.

THE PROPAGATION OF THE WAVE OF CONTRACTION. The normal contraction is started in the sinus venosus, propagated to the auricles, thence to the ventricle, and finally to the bulbus aortæ. Between the contractions of each of these cavities there is a slight pause, whereas the contraction spreads so rapidly over each cavity that all parts, say of the auricles or

ventricle, appear to contract simultaneously. It is obvious that the excitatory wave might be propagated through the heart, either from one muscle cell to another, by or means of nerve fibres which would excite the muscular tissue of each cavity to contract.

That the propagation cannot be due to any nerve trunks running from

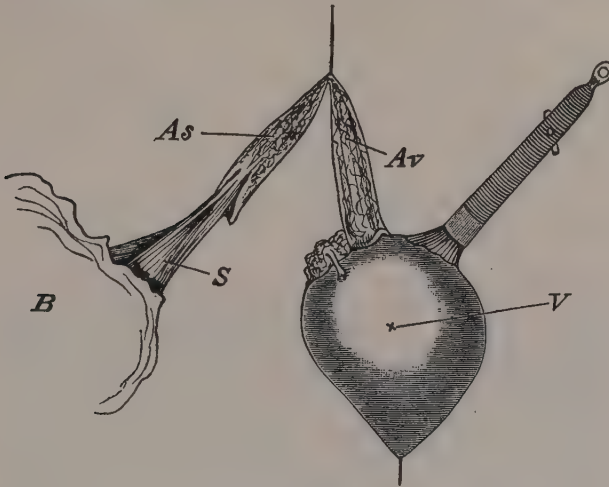


FIG. 350. Heart of Tortoise with Auricle slit up so as to cause a Partial Block. (GASKELL.)

sinus to ventricle is shown by various experiments of Engelmann and Gaskell. Thus, if the auricle is slit up by a series of interdigitating cuts, the contraction wave starting from the sinus travels along the auricular muscle around the end of each section and finally, on arrival at the ventricle, causes a contraction of this cavity. In the heart of the tortoise, the nerve trunks run in the band of tissue joining the sinus to the ventricle; this band, with all its contained nerves, can be excised without interfering in any way with the normal sequence of contractions.

The pause observed between the contractions of auricles and ventricle has been shown by Gaskell to be due to the retardation of the excitatory wave which occurs in its propagation through the muscular tissue in the auriculo-ventricular junction. A similar retardation of the wave can be produced at any point, in either auricles or ventricle, by diminishing the conducting muscular tissue to a sufficiently small amount. Thus, if the auricle of the tortoise be divided as in the diagram (Fig. 350), it will be noticed that the sinus first contracts, then the auricular half *As*; a distinct pause then occurs while the contractile process is passing over the 'bridge,' and finally *Av* contracts, followed by the ventricle. The normal pause between the contraction of the auricles and ventricle is due, therefore, to a partial 'block' at the auriculo-ventricular junction. If the block be increased in the experiment just quoted, as for instance by allowing the bridge of tissue to dry or by making it still narrower, it may be found that only one out of every two contractions passes across the bridge (Fig. 351),

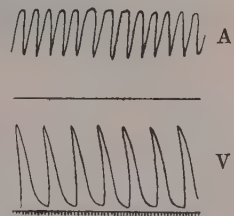


FIG. 351. Contraction of Auricles and Ventricle of Tortoise Heart. The auriculo-ventricular groove has been clamped so as to produce a partial block allowing only every second contraction to pass. (GASKELL.)

and the slightest increase in the resistance to the propagation of the wave may lead to the block becoming complete.

The wave of excitation is believed to pass from cell to cell of the cardiac muscle by means of the intercellular bridges with which these interconnect.

By the methylene blue method it is possible to demonstrate a close network of non-medullated fibres surrounding all the muscle cells of the heart. It is obvious that the experiment just quoted would not exclude the possibility of propagation occurring through such a nerve network. The properties of the network would have to differ from those of any of the nerve tissues with which we are acquainted; for example, the velocity with which the excitation is forwarded is much slower than that in nerve. Moreover, we know that under certain circumstances impulses may be transmitted from fibre to fibre, even in striated muscle, and such a mode of propagation is the most obvious explanation of the phenomena observed in the heart.

The progress of the excitatory wave is well seen if a record be taken of the electrical changes resulting in the frog's heart from a single stimulation. A

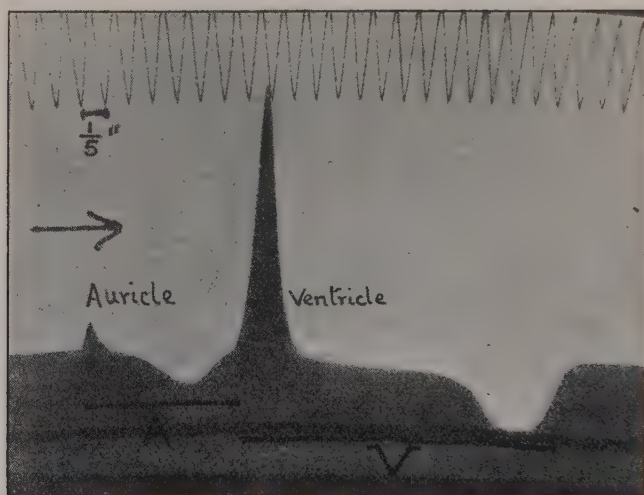


FIG. 352. Capillary Electrometer Record of Electrical Variation of Spontaneously Beating Tortoise Heart. (GOTCH.)

series of electrical changes occurs, which can be interpreted as due to the passage of a wave of excitation from the base to the apex of the heart, in accordance with the principles explained in Chapter XI.

Analogous effects are obtained on leading off the spontaneously beating heart in the frog or tortoise (Fig. 352). Since the excitatory process extends in the form of a wave to all parts of the heart, it is evident that the musculature of the heart is to be compared, not with skeletal muscle composed of many fibres, but to a single muscle fibre in which all parts are in functional continuity.

THE PROPERTIES OF CARDIAC MUSCLE

Since both the rhythm of the heart and the propagation of the contraction from one cavity to the next are functions of the cardiac muscle, a further consideration of the properties of this tissue is essential to enable us to decide to what extent the behaviour of the heart under varying conditions may be referred to the elementary properties of its muscular wall. Knowing the part played by the muscular tissue, we shall then be in a position to discuss

the various nervous and chemical agencies by which the activity of the muscular tissue is modified and brought into relation with events occurring in other parts of the body.

RESPONSE TO DIRECT EXCITATION. If the beat of the frog's ventricle, or of a strip of mammalian ventricle, be recorded, the curve obtained closely resembles the twitch of a voluntary muscle, except that it occupies a longer time; the contraction of the mammalian ventricular muscle lasts three-tenths of a second, of the frog's ventricle about half a second, and of the tortoise ventricle about two seconds.* The contractile process originates at the stimulated point and travels thence to all other points. If a ventricle strip, or the frog's ventricle rendered motionless by a Stannius ligature, be stimulated with a single induction shock, if it responds at all it will respond with a maximal contraction, no change in the extent of the contraction being obtainable, however the stimulus may be increased. There is thus no proportionality in the heart between strength of stimulus and height of contraction. We have seen that the response to a minimal stimulus in skeletal muscle is smaller than the response to a maximal stimulus, because in the former case only a small proportion of the muscle fibres is active, so that increasing the strength of the stimulus merely increases the number of fibres thrown into contraction, and a maximal contraction of skeletal muscle is one involving all the fibres. In the heart muscle all the muscle fibres are functionally continuous, so that a stimulus, if it excites at all, must excite all the fibres, and every contraction must be analogous to the maximal contraction of a skeletal muscle. The 'all or none' law in any contractile tissue is therefore only obvious without special methods when, as in heart muscle, there is functional continuity between all the contractile elements.

SUMMATION OF STIMULI. If an isolated frog's ventricle which is not beating be stimulated with inadequate shocks, it may be found, on repeating these shocks at short intervals of time, that they become adequate and cause a contraction of the ventricle. A stimulus, therefore, which is subminimal may nevertheless cause some change in the heart muscle, so that the latter responds more readily to subsequent stimuli.

A similar improving effect of previous stimulation on the condition of the heart muscle may be observed on the contractions themselves. Thus in a 'Stannius preparation,' if the ventricle be excited with single induction shocks once in every ten seconds, the first four or five contractions form an ascending series, each contraction being rather higher than the preceding one. This is often spoken of as the 'staircase phenomenon' (Fig. 353). Each of the contractions represents a maximal contraction, but this maximum effort is at first not so great as it becomes after a few previous contractions.



FIG. 353. Group of Pulsations showing 'Staircase' character.

THE REFRACTORY PERIOD. We have seen that, when two stimuli are applied to a skeletal muscle, or to a nerve, at a sufficiently short interval of time, the second stimulus is without effect. In the case of muscle, the refractory period has passed away long before the muscle begins to respond, so that the stimulus applied after recovery from the refractory stage excites a second response, and wave-summation is produced. Repeated stimuli give a tetanus much larger in extent than the twitch evoked

* The duration of the contraction depends on the temperature. The figures given are for the mammalian heart at 37° C. and for the amphibian heart at about 15° C.

by a single stimulus. The phenomenon of the refractory period, which appears to be present in all forms of excitable tissue, was first observed in heart muscle. In this tissue the refractory period is extremely prolonged, and lasts as long as the contraction, whether this occurs spontaneously or is evoked by a single stimulus. Hence, during the whole time that the muscle is contracted, any stimulus, however strong, applied to it remains without effect. As the contraction passes away the irritability once more rises and, as in the case of nerve, passes through a super-normal phase before it returns to normal. Directly after the contraction, the excitability is so depressed that a very strong stimulus

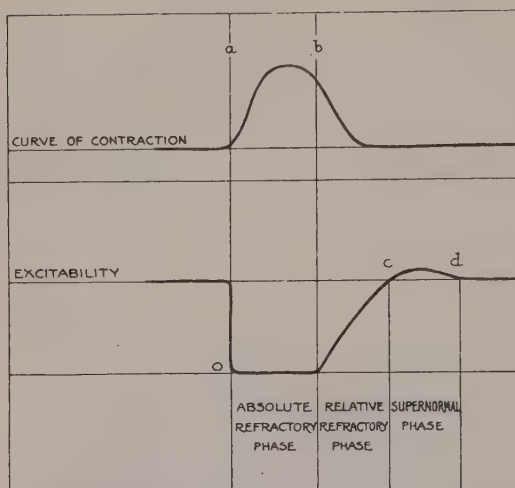


FIG. 354. Diagram showing changes in the excitability of heart muscle accompanying and following a single contraction.

is required to produce excitation, and the strength necessary for this purpose gradually diminishes as the excitability returns. We may thus distinguish two phases: (a) an *absolute* refractory period during which no stimulus, however strong, can produce excitation; (b) a *relative* refractory period, during which a second contraction is evoked by making the stimulus strong enough. The relation of these two phases in the excitability of cardiac muscle to the contraction produced by a single stimulus is shown in the accompanying diagram (Fig. 354). Directly after an effective stimulus is applied, the irritability of the preparation drops to zero and remains at this level during the phase of contraction. As relaxation of the cardiac muscle begins, excitability commences to rise, but some time elapses before it reaches normal. During this relative refractory period a second contraction of the muscle can be induced, the stimulus required being greater as it approaches the absolute refractory period.

We may imagine that, at each contraction of the heart muscle, there is a sudden decomposition of all its irritable material. As soon as this process comes to an end, the reverse process of assimilation or reformation of irritable material begins, and lasts throughout the diastolic period. In heart muscle contracting rhythmically, the store of irritable material would therefore be at its maximum just before each contraction. It is evident that the power of the heart muscle to contract in response to a stimulus must be at a minimum immediately after the automatic discharge has taken place, and will continually increase from this point as the store of irritable material grows, until it arrives at such a height that the discharge occurs spontaneously. Just before this spontaneous contraction the heart muscle would respond to a minimal stimulus.

We should therefore expect the length of the refractory period to depend on the duration of the excitatory process: the smaller the breakdown as the result of excitation, the shorter will be the subsequent absolute refractory period. A contraction excited during the relative refractory period will be

shorter than normal, because there has been less time for the accumulation of irritable material. Hence if the heart is stimulated to beat more frequently, the absolute refractory period following each beat is shortened, and we find that the length of the refractory period is inversely proportional to the frequency of the beat.

Thus Lewis found the following duration of the absolute refractory phase in mammalian auricular muscle under different rates of excitation :—

Rate	Refractory phase duration
100	0.2 sec.
130-140	0.15 to 0.17 sec.
290	0.08 to 0.11 sec.

The refractory period is also shortened by stimulation of the inhibitory nerve to the heart, namely the vagus. This also will have the effect of diminishing the extent of the discharge at each beat. Thus the length of the refractory period seems to be determined by the amount of energy liberated or by the extent of the breakdown of irritable material in the previous contraction.

Under certain conditions the refractory period appears to be abnormally prolonged owing to the fact that a contraction is initiated by the second stimulus, but does not spread to the whole of the muscle, and hence is concealed (Drury and Love). This increase of the *effective* refractory period is seen when the muscle is subjected to cold, pressure, acid solutions, veratrine or quinidine, some of which, *e.g.* veratrine, do not alter the absolute refractory period at all, while others, *e.g.* quinidine, increase the absolute refractory period, but not to such an extent as might be supposed from estimations of the effective refractory period.

When a tracing is being taken from part of the heart, *e.g.* the ventricle, which is beating at its normal rhythm in consequence of a stimulus communicated to it from the sinus venosus, it is found that the application of a single shock to the ventricle early in its diastole, is followed by the appearance of a ventricular contraction some while before the normal one would be due. This is called a *premature contraction* (or, less accurately, an 'extra systole'), and is followed by a 'compensatory pause' (Fig. 355), and in certain cases the first contraction after the pause is considerably augmented. This is due to the fact that one of the impulses travelling from the sinus arrives at the ventricle during the refractory period ensuing on the application of the artificial stimulus; hence it produces no effect and the ventricle has to wait for the arrival of the next succeeding excitatory wave from the sinus before it gives its next beat. Hence the compensatory pause does not occur when we are testing the effects of artificial stimuli on the sinus venosus.

On account of the refractory period which ensues on the commencement of the contractile process in heart muscle, it is impossible to throw the muscle into a tetanus, since all the stimuli which fall during systole are entirely ineffective. By using very strong stimuli it is possible to intercalate premature contractions before the heart has returned to the base line, *i.e.* before diastole is complete. So that in this way one may obtain an almost continuous contraction (presenting, however, waves on its summit), which differs from the tetanus of skeletal muscle in the fact that its height is no greater than the height of a single contraction.

Only when the functional continuity of the heart muscle is impaired by the 'block' effect of vagal stimulation or by the administration of muscarine is it possible to obtain phenomena even superficially analogous to the summation of contractions in skeletal muscle.

INVERTEBRATE HEARTS. The hearts of invertebrates are often very different in structure and properties from those of the higher animals. In *Helix* the heart is composed of plain muscle, while in *Limulus*, which has been extensively studied by

Carlson, the heart forms a segmented tube of ordinary striated muscular fibres, which has a local system of ganglion cells, but so situated that they can be cut away entirely



FIG. 355. Tracings of Spontaneous Contractions of Frog's Ventricle, to show Refractory Period. (MAREY.)

In each series the surface of the ventricle was stimulated by an induction shock at *E*, as indicated by the tracing of the signal. In 1, 2 and 3, this stimulus had absolutely no effect, since it fell during the refractory period. In 4, 5, 6, 7 the effect of the shock was to interpolate a premature contraction in the series, the latent period (shaded part) gradually diminishing from 4 to 7 (diastolic rise of irritability). In 8 the irritability of the preparation was already considerable, and the latent period inappreciable. The 'compensatory pause' after the premature contraction is also well shown in 4, 5, 6, 7, 8.

from the muscular portions of the organ. The arrangement of the cardiac nervous system in *Limulus* is shown in Fig. 356.

Extirpation of the nerve cord abolishes spontaneous contractions. It is possible to

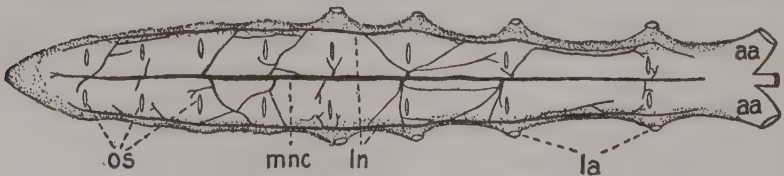


FIG. 356. Heart of *Limulus* from Dorsal Surface. (CARLSON.)
mnc. Median nerve cord. *ln*. Lateral nerve trunks.

make a nerve-muscle preparation of the anterior part of the heart, consisting of the muscle of the first two segments with a longer stretch of the lateral nerves (Fig. 357). Stimulation of the lateral nerves with a single shock causes a single beat of the anterior segments; tetanising shocks cause a continued contraction of the muscle preparation.

There seems to be no doubt that in this animal the beat of the heart is originated and co-ordinated by the action of the local ganglionic centres.

The heart muscle does not show a prolonged refractory period, and on direct stimulation with repeated shocks there may be a complete tetanus.

It would, for these and similar reasons, be wrong to transfer the results obtained on the heart of *Limulus*, or other invertebrates, to the explanation of the phenomena exhibited by the hearts of vertebrates.

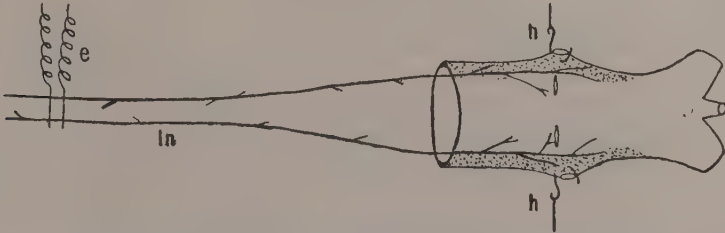


FIG. 357. 'Nerve-muscle Preparation' of Heart of *Limulus* consisting of the Muscle of the two Anterior Segments, with the two Lateral Nerves. (CARLSON.)

THE CONTRACTION OF THE MAMMALIAN HEART

In the mammal the two sides of the heart are in communication only by means of the blood vessels of the systemic (including the coronary) and pulmonary circulations. Each side consists of an auricle into which the veins open, and a ventricle which receives the blood from the auricle and discharges it into the arterial trunk—either aorta or pulmonary artery. Since the auricles have to act merely as a receptacle for *part* of the blood which enters during the relaxation or diastole of the heart, their cavities are smaller than those of the ventricles, and their walls are thin, corresponding to the small amount of work thrown on them in propelling blood into the relaxed ventricle. The ventricles have the office of carrying on the main work of the circulation, viz., of forcing blood through the peripheral resistance. Their walls are much thicker than those of the auricles. The right ventricle has a wall which is only about one-fourth the thickness of the left ventricle, in conformity with the much heavier work to be done by the latter. The capacity of both ventricles is approximately equal, and amounts in man to about 140 c.c. for each ventricle when the heart is completely relaxed.

The auricles are separated from the ventricles by a fibro-tendinous ring. From this ring take origin most of the muscular fibres of the heart walls.

The muscular fibres of the auricles run in both circular and longitudinal directions, the circular fibres being continued round both auricles, and special rings of circular fibres surrounding the openings of the great veins. From the fibro-tendinous ring between the auricle and the left ventricle and from the sides of the aorta, the muscular fibres forming the superficial layer of the ventricular wall pass obliquely downwards to the left towards the apex of the ventricle. Here they loop round into the interior of the ventricle and pass up near its inner surface to end either in the papillary muscles or in the auriculo-ventricular ring of fibrous tissue. Between these two layers we find a third median layer of muscular fibres which is in the form of a muscular cone. The fibres of this layer form complete loops round the left ventricle. The middle layer is connected by many strands of muscular fibres with both inner and outer layers.

Mall divides the muscular fibres of the mammalian heart into four groups, two superficial and two deep, as follows (Fig. 358):

(1) The *Superficial Bulbo-spiral Fibres*. These arise from the *conus arteriosus*, the left side of the aorta and the left side of the auriculo-ventricular ring, and take an oblique course to the apex, where they make a spiral turn (the *vortex*) and reach the interior of the left ventricle, ending for the most part in the interventricular septum and the papillary muscles.

(2) The *Superficial Sino-spiral Fibres* rise on the dorsal side of the heart from the right auriculo-ventricular ring and run obliquely on the anterior surface of the right

ventricle to the apex, where they also turn inwards, forming the anterior horn of the vortex, and end chiefly in the papillary muscles of the right ventricle.

(3) The *Deep Bulbo-spiral Fibres* form a complete cylinder around the left ventricle, and are attached chiefly to the dorsal side of the aorta.

(4) The *Deep Sino-spiral Fibres* are attached to the dorsal aspect of the left auriculo-ventricular ring, whence they enter the right ventricle and turn upwards towards the base. The uppermost of these fibres form circular rings round the *conus arteriosus* at the base of the pulmonary artery.

The mammalian heart will beat for some time after it has been cut out of the body, and a perfectly rhythmic activity may be maintained for hours by

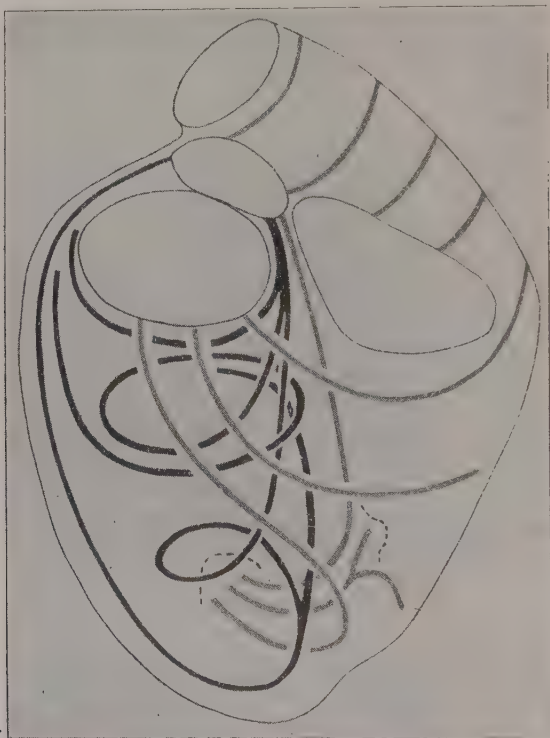


FIG. 358. View of the Heart from behind, to show the Course of the Chief Strands of Muscle Fibres. (MALL.)

The black lines represent the *bulbo-spiral* fibres, the grey lines the *sino-spiral* fibres.

feeding it from the coronary arteries with a suitable oxygenated perfusion fluid, as will be described later.

The ventricles of mammals are endowed with great rhythmic power, and it is possible to sever or crush all the nervous and muscular connections between auricles and ventricles without stopping the contractions of the ventricles, which, after a pause, recommence beating at a rhythm which is independent of and slower than that of the auricles. A piece of an auricular appendix, suspended in warm oxygenated Ringer's solution, will continue to beat for hours, and a fragment of the ventricular wall, free from ganglion cells, will similarly contract if fed by an artificial circulation through a branch of the coronary artery. We may therefore conclude that in the mammalian as in the amphibian heart, every part of the heart muscle possesses the power of rhythmic activity, the normal sequence of the beats being determined by the greater frequency of the natural rhythm of the venous end of the heart.

The excitatory condition started at one point in the muscle spreads through the muscle in all directions, and the process of conduction of excitation seems to be independent of nerve fibres. As in the frog, the excitatory process may, in exceptional circumstances, be made to travel in a direction the reverse of normal, as, for instance, when the ventricles are excited at a rhythm of higher frequency than the natural beat which is starting at the venous end of the heart. It is difficult to conceive of an arrangement of neurones which would propagate impulses impartially in either direction. On the other hand the phenomena are easily explained on the assumption that the whole of the musculature of the heart acts in many respects as a single muscle fibre, along which an excitatory process may be propagated in any direction. But in the adult mammalian heart, on superficial dissection, the muscle fibres both of auricles and ventricles are seen to arise from a fibro-cartilaginous ring surrounding the auriculo-ventricular junction, leaving apparently no muscular continuity between the two cavities. On this account it was thought for many years that the propagation of the contraction from auricles to ventricles must occur by means of nerve fibres, and it was only with the discovery by Kent, and His of a distinct band of modified muscle fibres passing from the auricles to the ventricles, the '*auriculo-ventricular bundle*,' that an anatomical basis was furnished for the conduction of the wave.

The heart is developed from a muscular tube in which, as Keith has shown, we may distinguish five chambers:—the sinus venosus, the auricular canal, the auricle, the ventricle and the bulbus (Fig. 359). The musculature of these chambers is continuous throughout. In the adult heart, *e.g.* of man, the anatomical relations of the different cavities have become considerably modified in the course of development. The sinus venosus, *i.e.* the part where in the lower vertebrates the contraction wave takes its origin, is now represented merely by the termination of the superior vena cava and of the coronary sinus in the right auricle. These two veins are derived from the right and left ducts of Cuvier in the embryo. The sinus venosus is also represented by a small amount of tissue underlying the *tænia terminalis* of the right auricle, as well as by the remains of the Eustachian and venous valves. The auricular canal gives rise to the auricular septum and to the auricular ring surrounding the auriculo-ventricular orifice, and in some hearts it is prolonged into the ventricle as the intraventricular or invaginated part of the auricular canal.

In the adult heart two accumulations of more primitive tissue are found in the region corresponding to the sinus venosus of the embryo, and these are known as the *sino-auricular node* and the *auriculo-ventricular node*. They are composed of delicate interlacing fusiform fibres, faintly striated and em-

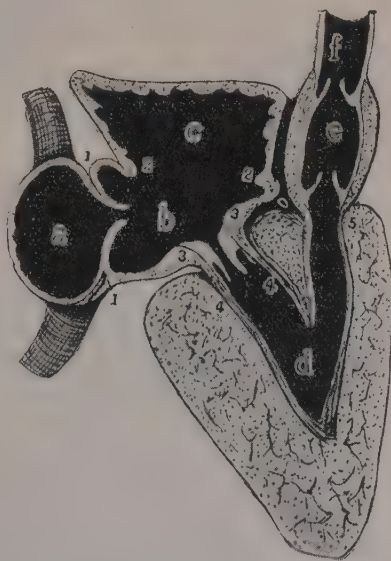


FIG. 359. A Generalised Type of Vertebrate Heart. (KEITH.)

- a. Sinus venosus.
- b. Auricular canal.
- c. Auricle.
- d. Ventricle.
- e. Bulbus cordis.
- f. Aorta.

- 1-1. Sino-auricular junction and venous valves.
- 2-2. Canalo-auricular junction.
- 3-3. Annular part of auricle.
- 4-4. Invaginated part of auricle.
- 5. Bulbo-ventricular junction.

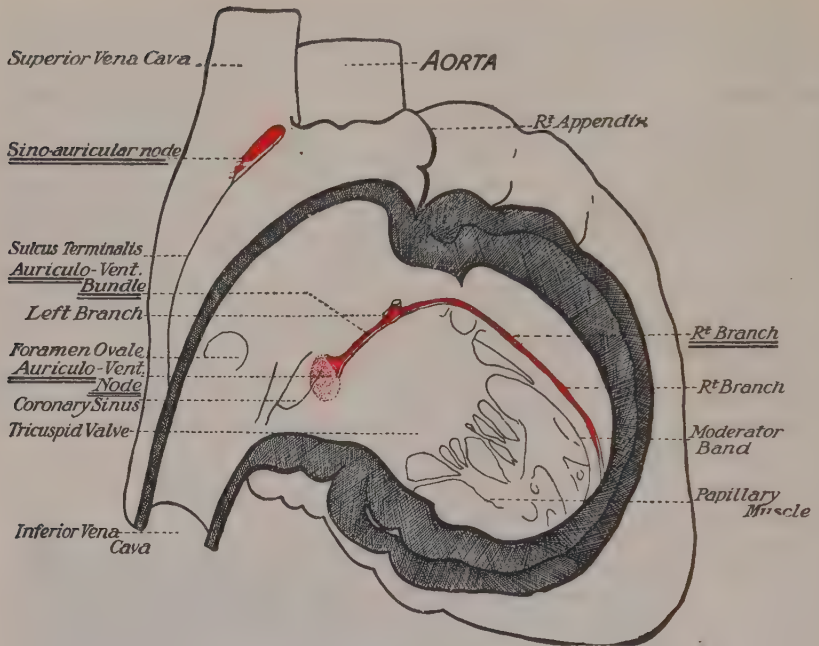


FIG. 360. Diagrammatic Representation of Course of A.V. Bundle.

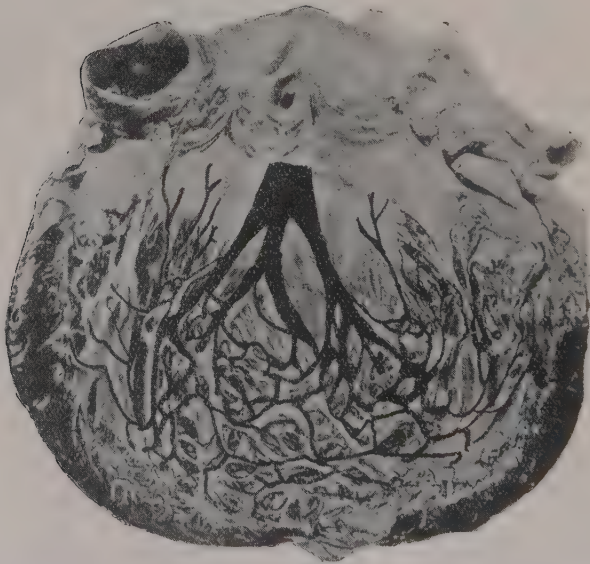


FIG. 361. Left Ventricle, laid open to display the Interventricular Septum, on which the Course of the Left Division of the Auriculo-ventricular Bundle and its Ramifications are shown in black. (After TAWARA.)

bedded in dense connective tissue. The fibres contain very little glycogen. The sino-auricular node (Fig. 360) lies in the groove between the superior vena cava and the right auricle. The auriculo-ventricular node lies at the base of

the auricular septum on the right side, below and to the right of the opening of the coronary sinus. From this point a bundle of muscular fibres (the *bundle of His*, or the auriculo-ventricular or A.V. bundle) runs along the top of the interventricular septum just below its membranous part and then divides into the right and left septal divisions, which pass down in each ventricle on the interventricular septum into the papillary muscle arising from the septum. Each half of the bundle gives off several branches which break up more and more, finally forming a reticulated sheet of tissue over the greater part of the interior of the ventricles just below the endocardium. The fibres composing this tissue are more primitive in character than the rest of the cardiac musculature and have long been distinguished as the 'fibres of Purkinje.' In them the fibrillation is confined to the periphery of the muscle cell. (Figs. 361 and 362). They are distinguished by a high glycogen content.

There are rich plexuses of nerves on the outer surface of the heart and also beneath the endocardium, and ganglion cells are freely scattered around the openings of the great veins, along the border of the interauricular septum, in the auriculo-ventricular groove and in the basal parts of the ventricles.

Numerous nerve fibres and ganglion cells are found to accompany the muscle fibres of the auriculo-ventricular bundle. We have, however, no reasons for regarding the nervous structures as concerned in the initiation or propagation of the excitatory wave.

The auriculo-ventricular bundle forms the only continuous muscular tissue between the auricles and ventricles, and destruction of it causes complete abolition of the normal sequence of beat between auricles and ventricles.

By leading off different parts of the heart to the string galvanometer, it is possible to determine the time relations of the excitatory process. It is then found that the sino-auricular node is the starting-point of the excitatory process concerned in each heart beat. It is therefore spoken of as the '*pace-maker*' of the heart. At each beat a contraction starts at the sino-auricular node, spreads a short way up the great veins, and along the auricular muscle in all directions (Fig. 363). When it arrives at the auriculo-ventricular node, the impulse is carried on to the ventricles along the auriculo-ventricular bundle, spreading along the branches of this bundle to almost all parts of the ventricular muscle. Although normally the sino-auricular node initiates each heart beat, this node can be put out of action by injury or great cooling without stopping the rhythmic sequence of the heart beat, the office of pace-maker being now taken up by the auriculo-ventricular node. A specialisation of function accompanies the differentiation in structure which we find in the auriculo-ventricular bundle and its branches. Lewis has shown that

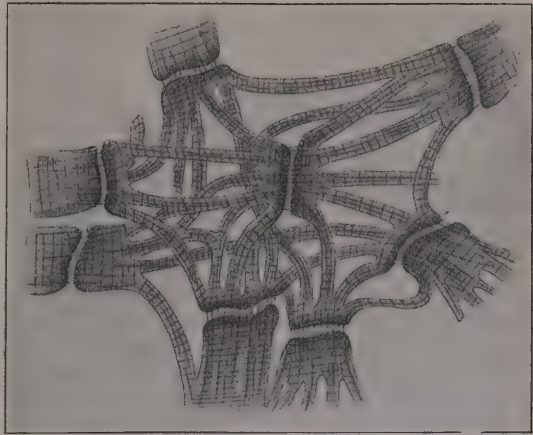


FIG. 362. Fibres of Purkinje, from the Sub-endocardial Network. (TAWARA.)

When it arrives at the auriculo-ventricular node, the impulse is carried on to the ventricles along the auriculo-ventricular bundle, spreading along the branches of this bundle to almost all parts of the ventricular muscle. Although normally the sino-auricular node initiates each heart beat, this node can be put out of action by injury or great cooling without stopping the rhythmic sequence of the heart beat, the office of pace-maker being now taken up by the auriculo-ventricular node. A specialisation of function accompanies the differentiation in structure which we find in the auriculo-ventricular bundle and its branches. Lewis has shown that

the conduction of the excitatory process along the auriculo-ventricular bundle of Purkinje tissue occurs about ten times as fast as the conduction through the ordinary muscular tissue of the heart, the rates being about

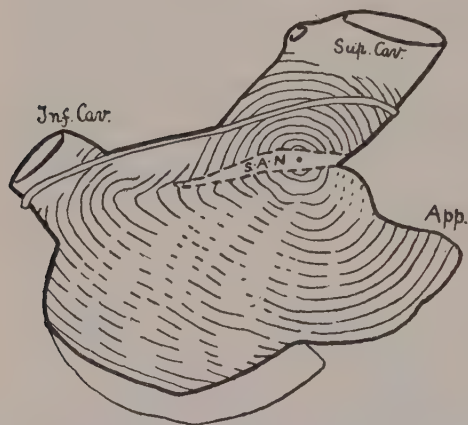


FIG. 363. Diagram showing the manner in which the Excitatory Process spreads from the Sino-auricular Node over the Auricles and along the great Veins. (T. LEWIS).

5000 mm. and 500 mm. per second respectively. Although all parts of the ventricles receive the impulse to contract almost simultaneously, the contraction wave, as judged by the electrical changes, is found to commence slightly earlier at two points, namely, on the anterior surface near the apex to the right of the groove separating right and left ventricles, and at the extreme apex of the heart where the endocardiac tissue comes very close to the surface. On the other hand, the conus arteriosus is the last part of the heart to begin contracting.

The limitation of the muscular continuity to a single narrow

FIBRILLATION OR DELIRIUM CORDIS. The great development of the refractory period in heart muscle renders it impossible to throw this tissue into a tetanus. When weak faradic stimuli are applied to the frog's ventricle, most of the stimuli fall during the refractory period, and only a certain number of stimuli become effective as the refractory stage following each contraction passes away. If, however, strong faradic stimuli of 20 to 50 per second are applied to the auricle or ventricle of a heart beating normally, the rhythmic contraction of the chamber stimulated ceases instantaneously; the chamber dilates and its walls are seen to be the seat of vermicular movements, each muscle fibre or fasciculus seeming to be contracting independently of the fibres around it, so that the whole surface is affected with a writhing movement. The same condition of fibrillation or delirium cordis may be produced in the mammalian ventricle by ligature or obstruction of one coronary artery, and this phenomenon may account for the sudden death which frequently occurs as a result of disease of the coronary arteries. It seems probable that a similar condition is sometimes responsible for the sudden death which may occur during the induction of chloroform anaesthesia (Levy).

When fibrillation is induced in the auricles by strong faradic stimulation, it generally passes off after a variable time and the ordinary rhythmic contractions recommence. In the ventricles of the larger animals this condition is irreversible. Fibrillation of the auricles is a frequent complication of heart disease, where the myocardium has been injured by some previous infective process, such as rheumatic fever. The fibrillation is at the rate of about 450 per minute, and does not spread to the ventricles, but sets up

frequent and irregular excitations which travel along the A.V. bundle and cause a rapid and irregular ventricular rhythm. The smaller contractions in this rhythm may be ineffective for the expulsion of blood from the ventricles, and merely promote the exhaustion of a heart which is probably already affected by the original disease. In the early stages of such cases the auricular fibrillation may occur in paroxysms which pass off, but sooner or later it tends to become permanent.

In some instances the auricular fibrillation is not general, and the effect of the local fibrillation is to impart a very rapid, but regular, rhythm to the auricles, while the ventricles have a regular rate one-half or a quarter that of the auricles. This is called *auricular flutter*.

The clue to the causation of fibrillation was given by observations of Mines and of Garrey. Mines found that under certain conditions a ring of frog's ventricular muscle might respond to a single stimulus by a wave of contraction passing continuously round the ring, and Garrey observed the same phenomenon in a ring cut from the contractile tissue of the umbrella of the jelly fish. The way in which this circus movement is brought about has been elucidated by T. Lewis. In Fig. 364 is represented a ring of auricular tissue. If it is excited rhythmically at X, the wave of excitation will travel in both directions round the ring and finish at Y. If, however, the rate of stimulation be continually increased, a time will arrive at which any slight difference in the duration of the refractory stage at *a* and at *b* becomes important. Let us suppose it is shorter at *b*. The wave due to the second stimulus may therefore be able to pass *b* but not *a*. The wave will thus pass in one direction only (anti-clockwise), and will travel right round the ring. By the time it has travelled past Y and arrived at *a*, the refractory stage may have passed off, so that the muscle at *a* can now contract. Whether the circus movement continues indefinitely will depend on (1) the rate of conduction, (2) the length of the ring, and (3) the duration of the refractory period. Anything which diminishes the rate of conduction and the duration of the refractory period (and both these changes result from frequent stimulation) will tend to set up a circus movement.

Lewis assumes that when fibrillation is present, there is a circus movement in a ring of tissue round the mouths of the great veins. This ring is not, however, separated from the rest of the auricle, so that the wave of excitation in its course round the ring will excite in turn the adjacent portions of the auricular muscle, so that these will contract at all intervals after the passage of the wave past X. All co-ordinate movements will then be abolished and the auricle will continue in a state of fibrillation. This explanation is supported by the fact that it is possible to set the auricle into fibrillation by the application of two shocks at such an interval that the second falls just outside the absolute refractory period of the auricular muscle, and the same thing doubtless occurs when the auricle or ventricle is set into fibrillation by the application of strong faradic currents. Administration of quinidine puts a stop to auricular fibrillation in about 50 per cent. of cases, and this is owing to the fact that it increases the effective refractory period.

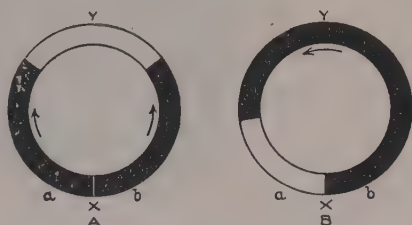


FIG. 364.

THE MECHANISM OF THE HEART PUMP

The normal direction of the blood flow through the heart is determined mainly by the arterial and auriculo-ventricular valves. The auriculo-ven-

tricular valves are membranes attached round the entire circumference of the auriculo-ventricular ring (Fig. 365). They are composed of fibrous and elastic tissue covered on each side with endocardium, and project downwards into the cavities of the ventricles. On each side the membrane is divided by deep incisions into large flaps, three in number on the right side (the tricuspid valves) and two in number on the left side (the mitral valves). The sail-like margins of these valves are connected by thin tendinous cords to the papillary muscles, which are nipple-shaped projections of the muscular walls of

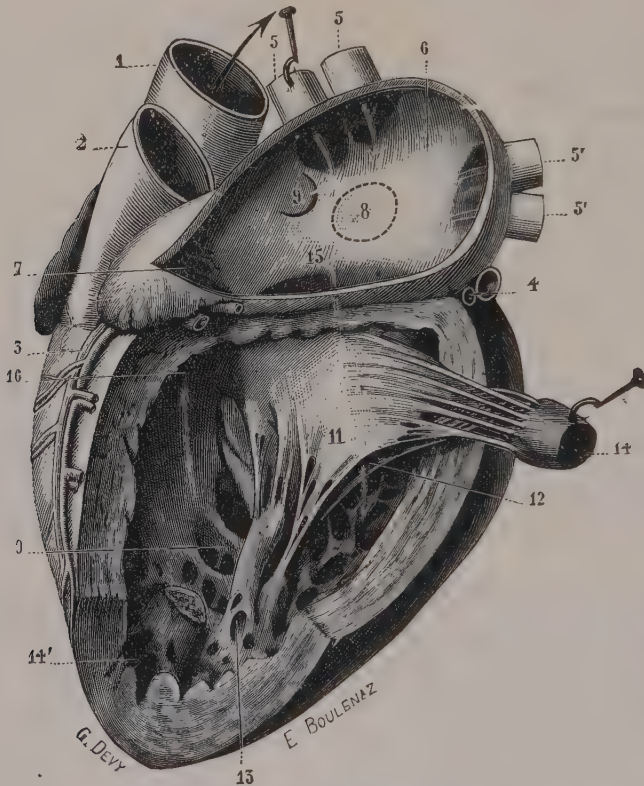


FIG. 365. Left Auricle and Ventricle, with Outer Side cut away to show Chief Points in Anatomy of Heart. (TESTUT.)

- | | |
|---------------------------|---------------------------------------|
| 1. Aorta. | 7. Auricular appendage. |
| 2. Pulmonary artery. | 10. Cavity of left ventricle. |
| 3. Ant. coronary vessels. | 11, 12. Mitral valves. |
| 5, 5'. Pulmonary veins. | 13, 14. Papillary muscles. |
| 6. Left auricle. | 16. Arrow pointing to aortic orifice. |

the ventricles. By this means the edges of the valves are kept close together and prevented from eversion under the strong pressure exerted by the contracting ventricle. By the downward pull of the papillary muscles on the valves during the contraction of the ventricles, closure is rendered more complete, the inner surface of the valves being apposed over a considerable area. The action of the valves is aided by the contraction of the fibres surrounding the base of the heart, so that the auriculo-ventricular orifice is much smaller during systole than during diastole.

From a purely mechanical standpoint the valves guarding the arterial orifices are much more perfect than those just described, which depend for

their efficiency on the proper contraction of the ventricular wall and of the *musculi papillares*. Each orifice is provided with three valves, each of which is semilunar in shape and is attached by its convex borders to the arterial wall, and presents in the middle of its free border a small fibro-cartilaginous nodule, the *corpus Arantii*, from which fine elastic fibres pass to all parts of the valve. The extreme margin of the valve, the *lunula* on each side of the corpus Arantii is very thin, being formed of little more than the endocardium. Whenever the pressure in the arteries is greater than that in the ventricles, these valves are closed, and the thin margins come in contact with similar portions of the adjacent valves, so preventing the reflux of a single drop of blood. The borders of the valves under these circumstances come together in the form of a star composed of three lines at angles of 120° , the three corpora Arantii being pressed together at the centre of the star.

No valves are found at the orifices of the great veins into the auricles, a reflux of blood in this situation during contraction of the heart being limited by the contraction of the muscular rings round the veins, which slightly precedes the main auricular contraction.

The heart and the roots of the great vessels lie almost free in a special cavity, the wall of which is formed by a tough fibrous membrane, the pericardium. This is attached below to the central tendon of the diaphragm, and above to the arterial trunks. It is lined by a layer of mesothelium continuous with a similar layer covering the surface of the heart. The two surfaces are kept continually moist by the pericardial fluid, so that the heart can move freely within the pericardium without friction. One of the chief functions of the pericardium appears to be to check an excessive dilatation of the heart during conditions attended by a great rise of venous pressure.

THE SEQUENCE OF EVENTS IN THE CARDIAC CYCLE. Each beat of the heart appears to begin by a simultaneous contraction of both auricles, associated with a retraction of the auricular appendages, which become pale and bloodless. After a brief pause the contraction of the auricles is followed by that of the ventricles, and blood is thrown out into the large arteries. In clinical terminology, the term 'systolic' refers to the ventricular systole, so that 'pre-systolic' events occur during auricular systole. The contraction of the auricles lasts about a tenth of a second, that of the ventricles about three-tenths of a second. The period of total relaxation or diastole lasts about four-tenths of a second. During this cycle of changes the following events are taking place within the heart :

In the diastolic period the aortic valves are closed, and the auriculo-ventricular valves open. There is a continuous flow of blood from veins, through auricles into ventricles and, as the walls of both these cavities are relaxed, there is no impediment to the inflow of the blood unless the heart dilates very much and begins to stretch the pericardium. Under normal circumstances the diastole comes to an end before the restraining influence of the pericardium can be effective.

The contraction of the auricles drives their contents into the ventricles and so still further increases their filling, no resistance being offered by the flaccid wall of the ventricles. As the blood rushes from auricle into ventricle through the funnel-shaped opening of the membranous tube formed by the valves, eddies are set up in the ventricle tending to close the valves, so that they are held, by the resultant of the two opposing currents, in a condition midway between closure and opening.

The onset of the ventricular contraction is extremely sudden. There is a

quick rise of pressure in the ventricle, which presses together the flaps of the mitral or tricuspid valves, while the bases of these valves are approximated by the contraction of the circular fibres at the base of the ventricles. As the heart shortens in systole the papillary muscles also shorten, so that the valves are prevented from eversion into the auricles, while the blood is pressed, so

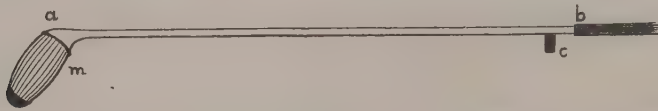


FIG. 366. Diagram of Marey's Cardiac 'Sound,' consisting of a long tube *a b*, terminating at one end in the ampulla *m*, which is covered with an elastic membrane. The side-piece *c* serves to indicate the position of the ampulla after it has been introduced into the vessel.

to speak, between the cone of the ventricular wall and the cone formed by the tubular valves.

The outflow of blood from the ventricles however, does not, commence immediately, and for a time, therefore, the ventricle is contracting on a closed cavity, and is thus performing an *isometric* contraction (isometric phase). Before the beginning of systole the pressure in the ventricular cavity is

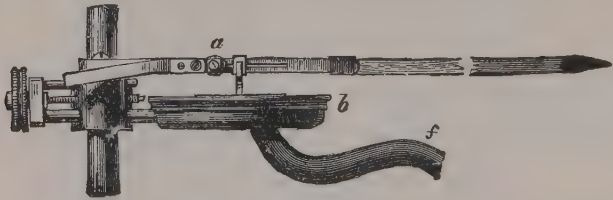


FIG. 367. Marey's Tambour.

a. Axis of lever. *b*. Metal tray covered with rubber membrane, and communicating by tube *f* with tube of cardiac sound.

quite small (only 2 or 3 mm. Hg.), while there is a pressure in the aorta of 70 to 90 mm. Hg. Before the aortic valves can be opened, the pressure in the left ventricle must rise to a point which is greater than that in the aorta, and similarly on the right side of the heart. As soon as this happens the valves open and the outflow of blood (ejection phase) commences, and continues so long as the pressure in the ventricles is higher than that in the great arteries.

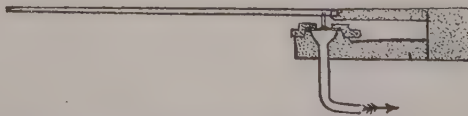


FIG. 368 Diagram to show Construction of Hürthle's Membrane Manometer.

Directly the ventricular pressure falls below the arterial pressure, the arterial valves must close again and the output of blood come to an end.

In order to obtain an accurate idea of the exact duration of each of these events in the cardiac cycle, it is necessary to study the changes occurring in the pressure within the auricles and ventricles during the various phases of the heart beat.

THE ENDOCARDIAC PRESSURE. A manometer which shall register accurately the changes in the pressure within the heart must be capable of responding to very rapid changes. Thus in the left ventricle at the beginning of the systole, there may be a rise of 130 mm. Hg in 0.06 sec.,

i.e. 2170 mm. Hg per sec. In a heart beating rapidly and forcibly under the action of adrenaline, the rise may be still more rapid, *e.g.* 150 mm. Hg in 0.025 sec. A mercurial manometer with its great inertia would be quite unequal to registering such rapid changes of pressure. We require an instrument with very small weight of moving parts, so as to possess small inertia and be capable of registering a rapid rise of pressure without entering into oscillations of its own.

Several methods have been adopted for this purpose. In the classical investigations of Chauveau and Marey a cardiac 'sound,' filled with air (Fig. 366) was passed down the jugular vein of a horse into the right auricle or ventricle, or down the carotid artery into the left ventricle. The sound was connected by a rubber tube with a Marey's tambour (Fig. 367) by which the pressure variations were recorded. Though the results were of great value, the recording system had serious defects which have now been largely overcome. A better instrument is a membrane manometer such as that of Hürthle. In this instrument (Fig. 368) the changes of pressure are recorded by the oscillations of a thick rubber membrane which covers a very small tambour. The tambour is filled with magnesium sulphate solution, which is also used to fill the tube connecting by an open end with the heart. This tube can be inserted in the same way as Marey's cardiac sound.

Even Hürthle's instrument is inadequate to give a correct representation of the very rapid changes of pressure occurring in the contracting ventricle. A study of the theory of recording instruments by Otto Frank has enabled him to lay down certain fundamental requirements of such a recording instrument. In order that an instrument may correctly reproduce rapid changes of pressure, the mass of fluid and of parts of the instrument moved must be as small as possible in order to reduce the momentum, and therefore the tendency to overthrow of the instrument, to the greatest possible extent. Moreover, in order to avoid vibrations of instrumental origin, the period of self-vibration of the mass moved must be as high as possible. This is accomplished, as in Hürthle's instrument, by using a very small tambour, covered with a strong, tightly stretched membrane connected, by as short and wide a tube as is feasible, with the heart or blood vessel where it is desired to register changes of pressure. The whole is filled with fluid. A lever is entirely got rid of, the minute oscillations of the membrane being recorded by means of a beam of light which impinges on a mirror attached to the rubber membrane and is reflected on, to a moving photographic surface.

Manometers on these principles have been designed by Frank, Wiggers, and Piper. Wiggers' manometer is shown in Fig. 369. At its lower end cannulae of various forms and sizes can be attached. At the middle of the tube is a short lateral tube to which, by a ball and socket joint B is attached a tiny 'segment capsule' A. Over the capsule is stretched a thick rubber membrane, to which on the straight side of the segment a small mirror is affixed. The entire capsule and its mirror can be adjusted in any direction by the handle D. A second small mirror E is carried on a small plate. This serves to project a base line, and is adjustable by the handle F. Alterations in the pressure within the manometer cause minute oscillations of the membrane, which can be recorded and magnified to any desired extent by means of a beam of light reflected from the mirror on to a moving photographic plate or paper (Fig. 370). The advantage of this optical method of registration is that the magnification can be increased to any extent without altering the mass moved. The 'figure of merit' of this manometer, *i.e.* its own period of vibration, when filled with fluid, is about 450 per second with a thick membrane, so that it can record with perfect accuracy all such rapid changes of pressure as may occur even in the left ventricle.

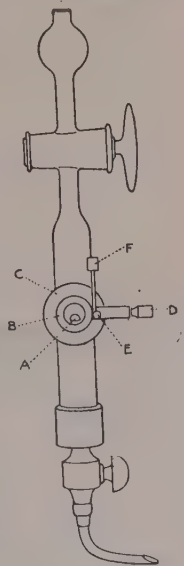


FIG. 369. Wiggers' Manometer, for Optical Recording of Blood Pressure (about one-third full size).

On registering the endocardiac pressure by the optical method, it is found that the curves vary in form according to the condition of the heart. In order to interpret these curves, we must utilise the knowledge obtained from a simultaneous record of the pressures in the auricle and ventricle,

or in the ventricle and aorta. Fig. 371 represents curves obtained from the left ventricle and left auricle. Very often the ventricular curve is not unlike the curve of contraction of the frog's heart muscle. Nearly always, however, it is possible to see on the up-stroke one or two elevations, the most

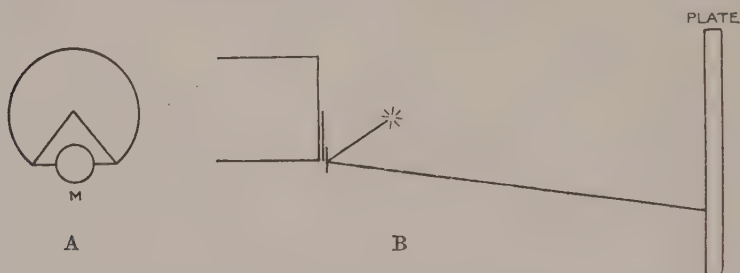


FIG. 370. A, Magnified Diagram of a 'Segment Recorder' covered with Membrane, to which is connected the minute Mirror M (front view).

B, Diagram showing how a Beam of Light is thrown on to the Mirror and then reflected on to a moving Photographic Plate.

noticeable being the elevation marked S_1 . This can be shown to correspond to the opening of the aortic valves.

The average course of the changes of pressure in the left heart during each beat is shown diagrammatically in Fig. 372. The cardiac cycle begins

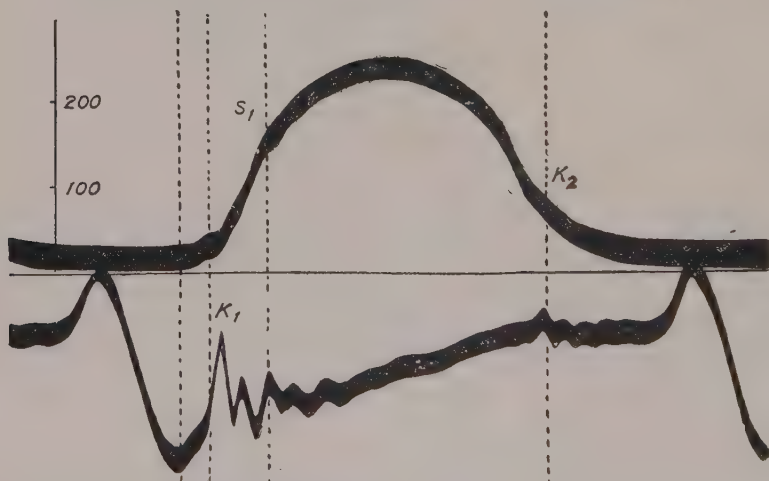


FIG. 371. Endocardiac Pressure Tracings, taken with Piper's Manometer.

Simultaneous tracings, the upper from left ventricle and the lower from left auricle. To be read from left to right.

K_1 Closure of A.V. valves.

S_1 Opening of aortic valves.

K_2 Opening of A.V. valves.

with the contraction of the auricle, which may or may not give rise to a slight rise of pressure in the ventricles. As the auricular contraction dies away, the ventricular contraction begins at I. This causes a very rapid rise of pressure. Almost immediately after the beginning of the rise the auriculo-ventricular valves close, and the isometric phase begins. The pressure then rises rapidly in the ventricular cavity without causing any change in its contents, or in the length of the muscle fibres. Directly the

pressure exceeds that in the aorta, the aortic valves open at the point marked II., where the ejection phase begins, and the aortic pressure thereafter rises with the ventricular pressure. During the whole duration of the ventricular contraction, the aortic pressure remains somewhat below the ventricular pressure, showing that blood is flowing continuously from ventricle into aorta. The ejection of blood is at first rapid, so that the pressure in the ventricles continues to rise. As the heart gets smaller, the amount of blood ejected into the aorta becomes less than that flowing out in the unit of time through the peripheral branches, so that the pressure begins to fall in the aorta and

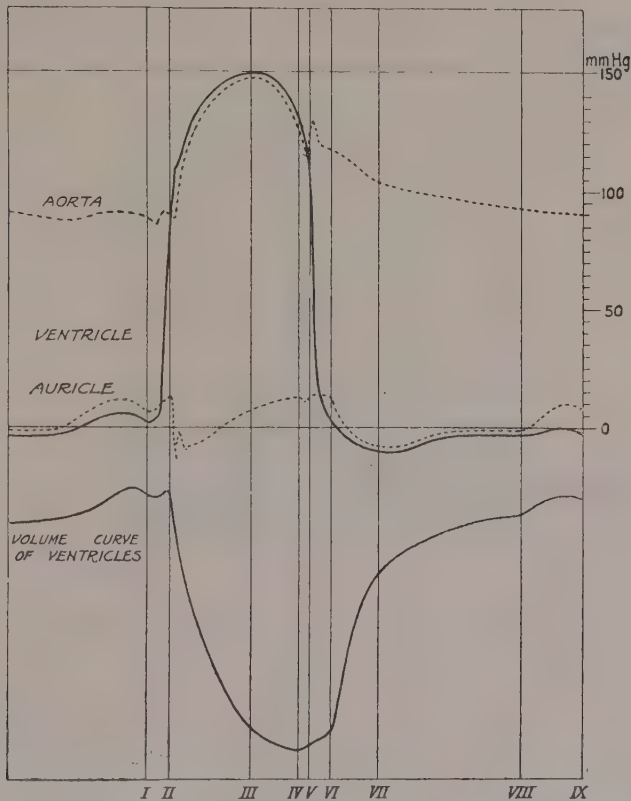


FIG. 372. Pressure Curves from Aorta, Ventricle and left Auricle, together with Volume Curve of the two Ventricles during one complete Cardiac Cycle. (Modified from WIGGERS.)

ventricle, even though the outflow of blood is still going on. The ejection period may therefore be divided into two phases, that of maximum ejection, and that of reduced ejection. Usually this portion of the curve forms a smooth arch, but under some conditions it may be flattened to form a plateau, of horizontal, ascending or descending slope. The ventricular muscle suddenly relaxes at the point marked IV., causing a sudden fall of pressure the ventricle, and a slight fall in the aorta. This latter, however, is arrested almost at once by the closure of the aortic valves, marked by the sharp depression, the *incisura*, in the aortic tracing. Between V. and VI. the relaxation is isometric, since all the valves guarding the orifices of the ventricle are closed. The pressure in the ventricle continues to fall, until at

the point VI. it drops below that in the auricle, and the auriculo-ventricular valves open, allowing the inflow of blood from pulmonary veins and auricle. The pressure in the ventricles then reaches the line of zero pressure, and remains at or near this line during the greater part of diastole. With a big inflow there may be a slight rise towards the end of diastole, which may be accentuated by the auricular contraction. If the chest is opened, the pressure in the ventricle never sinks below zero during any part of diastole. In the closed chest the pressure in the heart cavities during diastole may be negative, on account of the negative pressure within the thorax.

The time relations of these events naturally varies with the frequency of contraction of the heart. In the human heart, beating 75 times per minute, a cardiac cycle will last 0.8 seconds. The following may be taken as the average duration of the different phases in the left ventricle (Wiggers) :—

- (1) A small rise of pressure due to contraction of the auricles, lasting

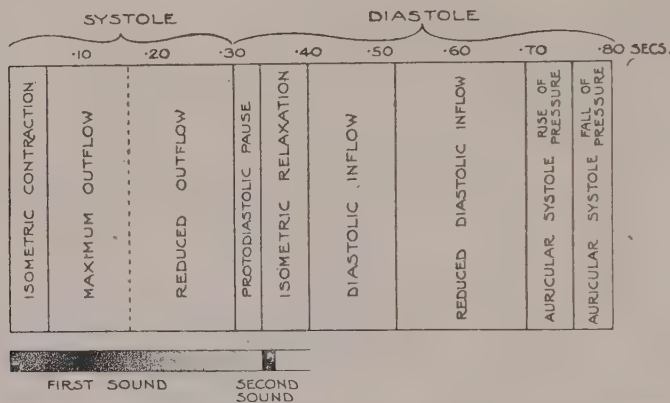


FIG. 373. Diagram showing average Time Relations of Events constituting a Cardiac Cycle.

0.05 second. The whole auricular systole (rise and fall of intra-auricular pressure) takes about 0.11 second.

- (2) The isometric phase lasts from 0.04 to 0.06 second.

(3) The total duration of ventricular systole is about 0.3 second, varying from 0.33 to 0.23, as the heart rate quickens from 60 to 120 per minute.

- (4) The diastolic phase may be divided into the following periods :—

- | | |
|--|---|
| (a) Protodiastolic phase (from beginning of relaxation to closure of aortic valves), 0.038 second. | } Total ventricular diastole
= 0.39 sec. |
| (b) Isometric relaxation, 0.076 second. | |
| (c) Rapid inflow phase, 0.113 second. | |
| (d) Slow inflow phase, 0.163 second. | |

The relative durations of these two last phases will naturally vary according to the rate of the heart and the amount of blood flowing into the heart in unit time.

The average relation of these various phases of the heart cycle are represented diagrammatically in Fig. 373. Similar but smaller pressure changes occur in the right side of the heart.

CHANGES OF PRESSURE IN THE AURICLES. Owing to the absence of valves between the right auricle and the venæ cavæ, changes of pressure within this cavity are transmitted along the veins. The venous pulsation is especially marked in circumstances which give rise to high venous pressure, so that the veins are not entirely emptied at any part of

the cardiac cycle. The most superficial observation shows that the jugular vein pulsates twice for each heart beat. The exact form of the pressure tracing in the auricles varies considerably, according to the inflow of blood and the state of filling of their cavities. A typical tracing with a moderate inflow of blood is given in Fig. 371, p. 718, and in this figure the relations of the different elevations in the auricular tracing to the intraventricular events can be made out. A somewhat different curve is given in Fig. 374, but it will be noted that the essential features of the curves are identical. In every case the auricular curve presents the following features :

- (1) The first positive wave (pre-systolic wave) corresponding to the auricular systole.
- (2) The second positive wave *k* (first systolic wave) occupying the begin-

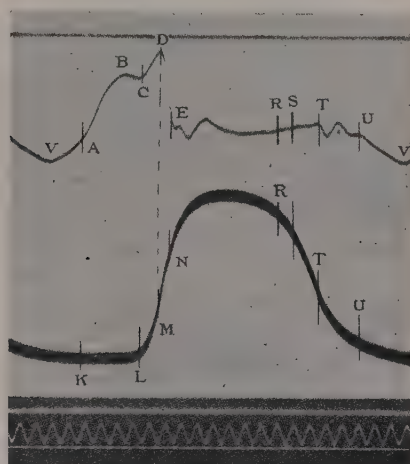


FIG. 374. Synchronous Left Auricular (upper) and Left Ventricular (lower) Pressure curves. (WIGGERS.)

A, B, C = Auricular systole. C, D = Second positive wave.
R = End of ventricular systole. U, V = Rapid inflow phase.
Time = 0.02 second.

ning of the ventricular systole. This is caused by the sharp closure of the mitral valve.

(3) A third positive wave (second systolic wave) which may present secondary undulations. This rise of pressure is due to the gradual filling of the auricles while the auriculo-ventricular valves are still shut.

(4) A negative wave. At this point the ventricle is entirely relaxed and the auriculo-ventricular valves open, so allowing the blood to flow freely from the auricle into the ventricle. This negative wave (U.V., Fig. 374) is not always well marked, and is represented only by a series of small undulations in Fig. 371.

The pressure rises in the left auricle somewhat higher than in the right auricle. In the latter case the big veins act as a supplementary reservoir to the auricle, so that in no period of the cardiac cycle need the pressure in the latter chamber rise to any extent. In auricular tracings the heart sounds are often apparent as small oscillations in the curve (Fig. 371).

NEGATIVE PRESSURE. In the tracings obtained by means of the older instruments, such as those of Hürthle, the lever at the end of the ventricular systole descended even below the base line, thus suggesting that for a short period of time there was actually a negative pressure in the ventricles. Many explanations were put forward to

account for this negative pressure, but they are all rendered unnecessary by the fact, revealed by more perfect graphic methods, that at no period in the cardiac cycle is there a negative pressure in the ventricles. Naturally, under normal conditions, the pressure in the chest outside the heart is negative owing to the elastic retraction of the lungs, and may vary from -3 to -30 mm. Hg, according as it is measured during normal expiration or during forced inspiration. This negative pressure may be transmitted to the interior of the heart, but the pressure within the ventricles never falls below the pressure obtaining outside the heart.

CHANGES IN FORM OF THE HEART. As the heart walls are perfectly flaccid during diastole, the shape of this organ as a whole will depend upon the position in which the heart is lying and the direction of its support. Thus if the chest and the pericardium be opened and the animal be in the supine position, the heart during diastole will be flattened from before backwards as a result of the simple weight of its contents. In this position, therefore, systole will be accompanied by a shortening in the lateral and vertical directions and a lengthening in the sagittal direction. During systole, when the heart becomes tense and all its fibres are firmly contracted, the heart, whatever its previous condition, takes the form of a truncated cone. Under normal circumstances the heart in the unopened chest lies in the pericardium, and is also supported laterally by the lungs, which, however, owing to their elasticity, have very little influence on its shape.

When the heart is freed from the pericardium, the obliquity of its fibres causes the apex to move forwards and to the right during systole; this movement is normally prevented by the attachment of the pericardium to the central tendon of the diaphragm, so that the most movable part of the heart comes to be the base. During systole the base of the heart moves downwards towards the apex. This movement is determined partly by the shortening of the fibres of which the ventricular wall is composed, partly by the lengthening of the great arteries as blood is forced into them under pressure from the ventricles. It was observed by Leonardo da Vinci that if three needles be passed through the chest wall so that their points lie, one in the base, one about the middle of the ventricles, and one in the apex of the ventricles, each ventricular systole is accompanied by a downward movement of the needle in the base of the heart, a slighter movement of the needle in the middle of the ventricles, and practically no movement at all of the needle which is thrust into the apex.

Even in the extreme contraction produced by heat rigor, it is found that the cavities of the ventricles are never entirely obliterated, though the right ventricle is reduced to a narrow slit widening out slightly in the neighbourhood of the auriculo-ventricular orifices, while in the left ventricle a distinct cavity is left between the mitral valves and the free ends of the papillary muscles. During normal activity the emptying of the cavities rarely proceeds to so great an extent.

THE CARDIAC IMPULSE. The movement of the heart at each contraction is communicated to the chest wall, over a limited area of which it may be felt and seen, except in fat individuals. The region where the pulsation of the chest wall is most marked usually lies in the fifth intercostal space, a little to the median side of the left nipple. This position is by no means constant, however, and may shift with alterations in the work of the heart, as after exercise. The pulsation is spoken of as the cardiac impulse or 'apex beat,' since it was formerly thought to be due to the twisting forward of the apex at each systole. The apex of the heart is really situated lower down, and is relatively motionless. During diastole the ventricles form a flabby flattened cone lying against the chest wall and slightly deformed by the latter,

especially when the subject leans forwards, or assumes the prone position. In systole the ventricles become hard and rigid, assuming the form of a rounded cone. This sudden recovery of shape and hardening of the ventricular wall pushes out that part of the chest wall in immediate proximity to the ventricles, and so gives rise to the cardiac impulse. The cardiac impulse, by its characters of force, regularity, frequency and maintenance, gives



FIG. 375. A Cardiograph. This is strapped round the chest, the central button is applied to the 'apex beat,' and its pressure on the chest wall regulated by means of the three screws at the sides. The tube at the upper part of the instrument serves to connect the drum of the cardiograph with a registering tambour such as that shown in Fig. 367.

valuable clinical information as to the occurrence and nature of the ventricular contraction.

The cardiac impulse may be registered by means of a cardiograph. In nearly all forms of this instrument a button resting on the chest wall transmits the movement of the latter to a tambour, which again is connected by a tube to a registering tambour. One such instrument is shown in Fig. 375.

The curves so obtained, which are known as cardiograms, may vary considerably in the same subject according to the pressure employed, the thickness of the chest wall and the exact spot at which the tambour is applied. Their interpretation often presents difficulties owing to the fact that their form is conditioned by two factors, viz. (1) the actual size (antero-posterior diameter) of the ventricles; (2) the resistance to distortion (*i.e.* the tension) of the ventricular wall; this factor will increase in importance with increasing pressure of the cardiograph button on the chest wall. Fig. 376 represents a cardiographic tracing or cardiogram which may be spoken of as typical. In order to interpret this curve we must record at the same time either the intraventricular pressure in animals or the heart sounds in man. This cardiogram presents considerable similarities to the endocardiac pressure curve. The exact point at which the auricular passes into the 'ventricular' contraction varies from case to case and may be altered by changing the degree of pressure put on the recording button. In the Figure given (Fig. 376) the auricular systole finishes before the main rise of the lever occurs. In many cases, however, the elevation due to the auricular systole may take up the greater part of the ascending limb of the curve. The great variability in the type of curve makes the cardiogram of little value for recording the different events of the heart cycle.

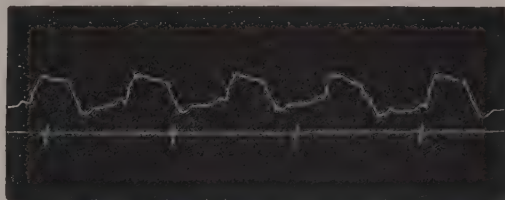


FIG. 376. Cardiogram. (HÜRTHELE.)

THE HEART SOUNDS. If we apply the ear, or listen with a stethoscope, to the front of a person's chest, we hear two distinct sounds accompanying each cardiac impulse, *i.e.* each systole, followed by a pause corresponding

to the diastole. The sounds are compared to the syllables *lubb, dup*, the first sound being low-pitched and prolonged, the second sound high and sharp. Thus the heart sounds may be represented: *lubb, dup, (pause), lubb, dup, (pause)*.

The causation of the second sound is very simple and may be considered first. It is heard most loudly just over the second right costal cartilage, *i.e.* the place where the aorta lies nearest the surface. It comes at the end of the systole, as determined by the cardiac impulse, and can be shown to be synchronous with the closure of the aortic valves. It is in fact caused by the sudden shutting and stretching of these valves, occurring directly the heart ceases to contract and to force the blood into the aorta. If the valves be hooked back in an animal by means of a wire passed down a carotid artery, the second sound disappears and is replaced by a murmur caused by the blood rushing back into the ventricle at the end of the systole. The same disappearance of the normal second sound is observed in cases where the valves are prevented from closing by diseased conditions.

The pulmonary and aortic valves generally close simultaneously. In some cases, however, the aortic may close slightly before the pulmonary, giving rise to a 'reduplicated second sound.' The pulmonary element of this sound is best heard over the second left cartilage, or in the second left intercostal space.

The first sound has probably a twofold origin, from the sudden closure of the auriculo-ventricular valves and from the contraction of the thick muscular wall of the ventricle.

If the veins going to the heart be clamped so that the heart can no longer be distended with blood nor the valves put on the stretch, the first sound is altered in character, but not abolished. The first sound may indeed be heard on listening with a stethoscope to the beat of an excised heart. It is said that two notes may be detected in the first sound—a high note of short duration due to closure of the valves, and a low-pitched note due to the muscular contraction. The muscular element of the first sound is probably less intense and of less definite pitch.

The distinctness with which the heart sounds are heard at the surface of the chest depends primarily on the physical conditions for conduction, such as the thickness of the chest wall, &c., but other things being equal, the loudness of the second sound varies with the pressure in the aorta or pulmonary artery, *i.e.* with the force with which the valve is closed, while the loudness of the first sound depends on the abruptness and force with which the ventricle contracts.

THE THIRD HEART SOUND. A number of observers have described a third heart

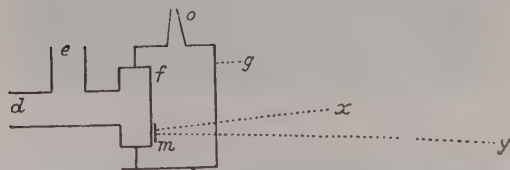


FIG. 377. Diagram showing construction of Wiggers' Capsule for the Direct Registration of Heart Sounds.

auricles to ventricles at the beginning of the diastole. The sound is shown objectively by the vibrations on the endocardial pressure curve given in Fig. 371.

THE GRAPHIC RECORD OF THE HEART SOUNDS. Various methods have been devised for graphically recording the heart sounds at the same time as other records, so as to display their relation to other events in the cardiac cycle. One method is to convey the

sound as occurring in certain individuals during the diastole, shortly after the second sound. It is softer and of a lower pitch than the second sound, and is heard most distinctly over the apex beat. It is probably due to the vibrations set up in the fluid itself, or in the auriculo-ventricular valves, by the sudden inrush of blood from

heart sounds to a microphone, which is thus set into vibration. The alterations in current so produced are recorded by a string galvanometer. The sound vibrations may also be recorded directly, by receiving them on a membrane carrying a small mirror, the vibrations of which are recorded photographically. Wiggers' instrument for this purpose is shown diagrammatically in Fig. 377. The segment capsule *f* is connected by a tube *d* with the bell of a stethoscope applied to the chest. The side tube *e*, which is adjustable, is to prevent the gross movements of the chest (apex beat) being transmitted to the membrane. The membrane is a delicate rubber film, formed by dipping the end of the capsule into rubber cement, which is allowed to dry. To it is affixed a tiny mirror *m*. To protect this membrane from extraneous sound vibrations it is enclosed in a housing *g*, having a front window of glass and a conical vent *o*, which serves the same purpose as the Eustachian tube of the middle ear, permitting equalisation of pressures on the two sides of the membrane. A record of the heart sounds obtained by this instrument is shown in Fig. 378.

CARDIAC MURMURS. When a fluid escapes through a narrow orifice into a wider space, vibrations are set up in the fluid and may be transmitted by any elastic medium to the ear, giving rise to the sensation of sound. The same sort of vibration may be set up in the large vessels or in the heart, whenever the blood passes rapidly through a narrow orifice into a wider space.

In the normal resting individual sounds produced in this way are so slight that they may be neglected; under abnormal conditions, as after diseases

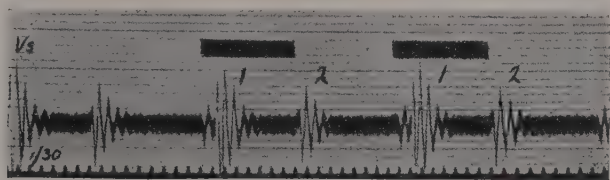


FIG. 378. Record of Heart Sounds. 1 and 2, first and second heart sounds. (WIGGERS.)

affecting the valvular orifices of the heart, or after exercise, this vibration may occur during every heart cycle and be heard with ease on applying the ear to the chest. These murmurs, or *bruits* as they are called, are of paramount importance in enabling the medical man to form a judgment as to the condition of the different valves of the heart. Thus injury to an aortic valve, so as to allow of leakage during diastole, allows a small amount of fluid under high pressure to pass from the aorta into the relaxed ventricle. On listening to the chest of a man with such a lesion, this regurgitation during diastole is heard as a rushing sound occurring in the place of or continuing the second sound up to the beginning of the next first sound, which denotes the commencement of systole.

In many cases, the disease which occasions the inadequacy of the valve is followed by cicatrisation, by which the valves become puckered and contracted and perhaps adherent, so that the orifices can never become thoroughly patent or thoroughly closed. Under such circumstances vibrations will also be set up in the current of blood as it escapes through the narrow orifice into the aorta during systole; and on listening to the chest over the second right costal cartilage, a 'to and fro' bruit is heard composed of a systolic immediately followed by a diastolic murmur. In the same way, incompetence of the mitral valve, or dilatation of the mitral orifice in consequence of weakness of the cardiac muscle, gives rise to a murmur which lasts during the whole of the ventricular contraction and is therefore *systolic* in character. Such a murmur is heard best over the area of the cardiac impulse, and is also trans-

mitted backwards so that it can be heard on listening at the back of the patient. A narrowing of the mitral orifice in consequence of contraction of the valves will set up a resistance to the flow of blood from left auricle to left ventricle. The auricle becomes hypertrophied, its contraction prolonged, and the escape of blood through the contracted orifices gives rise to a murmur which is heard on listening over the apex beat as a *presystolic bruit*. This bruit is easily distinguished from a systolic murmur by noticing that it runs up to and ends with the cardiac impulse, whereas a systolic murmur does not begin until the cardiac impulse commences.

THE HUMAN ELECTROCARDIOGRAM. Recent investigations by Craib have shown that when skeletal or other muscle is immersed in saline solutions, the electrical changes during excitation are not of the simple diphasic or monophasic nature obtained when the tissue is high and dry. Similarly, if we lead off any two parts of the heart's surface to a string galvanometer or capillary electrometer, we obtain movements which are caused, partly by changes occurring in the muscle just underlying the electrode, partly by changes occurring at a distance and transmitted by the intervening

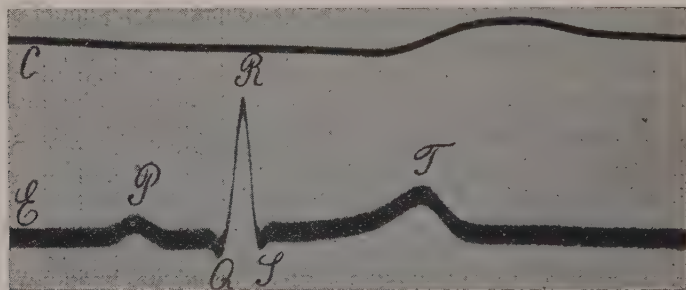


FIG. 379. Electrocardiogram of Man, obtained by Leading off from the Two Hands to a String Galvanometer.

c is the carotid pulse tracing. The different parts of the curve are designated by the letters P, Q, R, S, T, first applied to them by Einthoven.

muscle and blood acting simply as a moist conductor. These two kinds of effect may be alluded to as direct and indirect. If we lead off, not from the heart itself, but from neighbouring tissues in contact with the heart, we shall still obtain the indirect effects of the electrical changes at each heart beat, and these can be obtained when the intact animal is led off to the galvanometer by his limbs. In man, where the heart lies asymmetrically, it is usual to lead off the right arm and left arm, the right arm and left leg, or the left arm and left leg, the hand or foot being immersed in salt water, connected to the galvanometer by a zinc electrode contained in a porous pot full of saturated zinc sulphate solution. By this means an electrocardiogram is obtained similar to that shown in Fig. 379. The different points in a typical tracing, such as that contained in the figure, are designated by the letters P, Q, R, S, T, which were first applied to them by Einthoven and are retained because they do not involve any theoretical interpretation of the curves, which, in view of the reasons given above, would be difficult. Such interpretation as we have is the result of direct experimental observation, which shows that P is certainly due to the auricular contraction and Q marks the beginning of the ventricular contraction. The A.V. interval is given by the distance between P and Q, the total duration of the excitatory condition in the ventricle by the distance between Q and T.

Quite apart from the objections outlined above, we should not expect, in view of the mechanism of the propagation of the excitatory wave in the ventricle, that the cardiogram obtained in this indirect fashion would be easy of interpretation, at any rate so far as regards the course of the wave through the ventricular muscle. It must be remembered that the ventricular muscle is excited almost simultaneously at all points of its internal surface, in consequence of the rapid propagation of the wave of excitation along the branches of the A.V. bundle. The exact interval at which the excitatory process arrives at different points of the surface of the dog's ventricle after the upstroke of R in the whole electrocardiogram is shown in Fig. 380. The exact form and time relations of the ventricular part of the electrocardiogram may thus be altered in disease, or by interruption of one or other of the main branches of the A.V. bundle. The electrocardiogram, moreover, is of considerable use clinically for the determination of the relation between the auricular and the ventricular contractions.

The conductivity of the auriculo-ventricular bundle may be impaired by disease. In such cases, we get a series of phenomena, known under the name of Stokes-Adams' disease, the main characteristic of which is the slow contractions of the ventricle, accompanied by a rapid auricular wave in the venous pulse at a rhythm entirely independent of the ventricular pulse. The automatic activities of auricle and ventricle are, in fact, dissociated (heart block). At certain intervals or at certain stages of the disease, the fibres of the bundle may present only a partial block, so that the ventricle responds once to every second contraction of the auricle. The existence of this disease is shown at once on the electrocardiogram (or venous pulse, see Fig. 381) by the dissociation of the normal relation between the auricular and ventricular components.

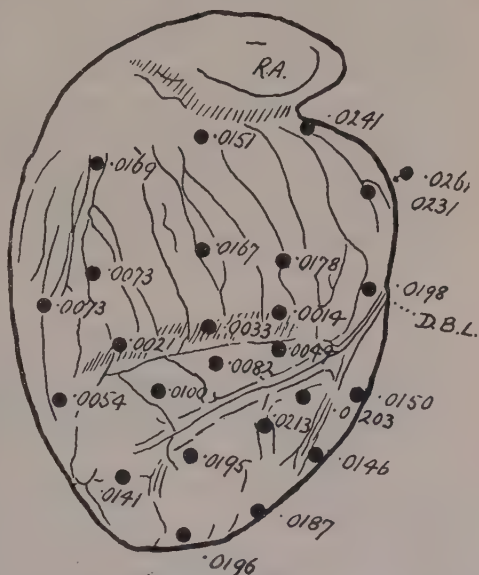


FIG. 380. Diagram showing the Time of Arrival of the Excitatory Wave at different points on the surface of the Ventricle in the Dog. (T. LEWIS.)

FILLING OF THE HEART IN DIASTOLE. The heart is perfectly flaccid during diastole and exerts no suction force on the blood in the veins. Its filling depends on the existence of a pressure within the veins greater than that in the auricles and ventricles; the greater the pressure within the large veins the more rapidly will the blood enter the heart during diastole and the larger the amount of blood in this viscus when it begins its contraction. In this process an important part is played by the mechanical conditions existing in the thoracic cavity. Owing to the elasticity of the lungs and the fact that they are constantly tending to contract, the pressure in the thorax is less than that of the external atmosphere by the amount which is required to distend the lungs to fill the cavity. At the end of expiration this difference amounts to about 5 mm. Hg, rising to 9 mm. Hg at the end of inspiration and to 30 mm. Hg at the end of a forced inspiration. This negative pressure is exerted on all the thoracic contents, but chiefly affects the thin-walled

veins and auricles, and the right ventricle when it is relaxed. On the other hand, the veins outside the thorax are exposed to a pressure which is a little above that of the atmosphere. When the thorax is at rest, the blood will flow from the extrathoracic regions, where the pressure is positive, into the big veins, auricles and ventricles lying within the thorax. The respiratory movements, by causing an alternating suction on the walls of the great veins and heart, act like an accessory pump and cause an aspiration of blood into the heart with each inspiration.

If the pressure within the thorax be raised enough to cause a sufficient positive pressure on the big veins and auricles, the return flow of blood to the heart comes to an end. Thus during extreme muscular effort the glottis is fixed and a positive pressure is produced in the thorax. The impaired circulation is rendered evident by the engorgement of the superficial veins and the blueness of the surface. Weber showed that, by a forcible expiration with the glottis closed, the pulse might disappear at the wrist and the circu-

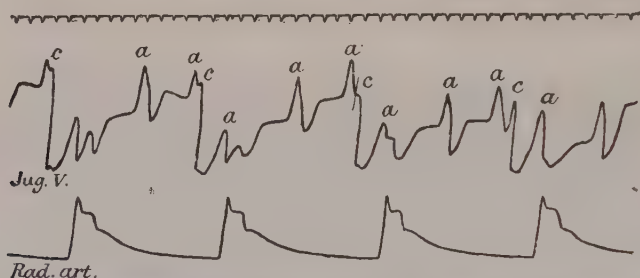


FIG. 381. Simultaneous Tracings of the Jugular Venous Pulse and the Radial Arterial Pulse, from a case in which the A.V. bundle was destroyed by disease. The contractions of the auricles are marked by the *a* waves on the venous pulse. They are more rapid than, and quite independent of, the ventricular contractions. (MACKENZIE.)

lation be brought to a standstill for such a time that loss of consciousness might supervene.

Since the heart during its systole diminishes its own volume by the expulsion of blood from the thorax, it becomes smaller, and the space thus provided in the chest cavity is taken up by an expansion of the veins, auricles, and lungs. To this systolic diminution of intrathoracic pressure is due the 'cardio-pneumatic' movements. These are recorded by attaching one nostril to a delicate tambour by means of a tube, while the other nostril and the mouth are kept closed. If a carotid pulse tracing be taken at the same time, it will be found that there is a fall of the lever attached to the nasal cavity, synchronous with the rise of the pressure in the arteries and due to the expulsion of blood from the heart.

The normal filling of the heart during diastole can be prevented by anything which hinders its expansion, such as the presence of fluid in the pericardial cavity. This happens in puncture of the left ventricle, as by rapier wounds. The same effect may be produced experimentally. If oil be injected into the pericardium in a dog with the chest open, when the pressure of the oil reaches about 60 mm., the pressure in the vena cava rises to a height just above that obtaining in the pericardial cavity. On increasing the pressure, a point is finally attained at which no more blood can be driven from the veins to the heart, so that the arterial blood pressure falls to zero and death ensues.

It is under such conditions that the *pulsus paradoxus* may be observed, in which the pulse becomes small or absent during inspiration. This is due to the fact that, when the pericardial sac is filled with fluid under a positive pressure, the auricles and ventricles

are much less affected by respiratory variations of intrathoracic pressure. The big veins, however, are still subject to these variations, so that during inspiration the blood tends to accumulate within them and not pass on into the heart. This organ therefore has less blood to discharge, and there is a diminution or absence of the pulse during inspiration. (Katz and Gauchat.)

The volume changes in the ventricles during the cardiac cycle can be investigated by the cardiometer, which will be described later.

In order to maintain the arterial pressure, it is necessary that the amount of blood driven into the arterial system by the contraction of the left ventricle should be exactly equal to that leaving the arteries to pass into the capillaries during the period which elapses between each systole.

The whole heart is enclosed in the tough, fibrous, inextensible sac formed by the pericardium. Under normal circumstances the heart, even during diastole, does not entirely fill the sac, increased rate of filling being compensated by a reflex quickening of the heart rate. Under extreme stress, when both inflow and resistance to outflow are increased, or when the heart muscle is in a bad condition from fatigue or disease, the heart may expand during diastole so as entirely to fill the pericardium, which then prevents any further distension, and, by limiting inflow limits also the systolic output of the heart. Thus, the size of the pericardium determines the maximum possible output per beat. If the pericardium be removed, the heart may dilate in diastole still further, and the only limit to its filling is set by the elastic resistance of the heart wall. Under these conditions the forcible contraction of the heart walls may rupture the muscle fibres and lead to the ultimate failure of the heart.

Many authors speak of a 'tone' of the heart muscle. This term is ambiguous. Tone ordinarily means a continuous contraction, and in the case of the heart such a contraction, on which the systoles would be superposed, would furnish a resistance to the distension of the heart and thus impede the inflow into the heart during diastole. In the auricle of the tortoise there is evidence of such a tonic contraction which undergoes rhythmic variations, but this is due to the existence of a layer of unstriated muscle fibres within the striated cardiac muscle of the auricular wall. There is no evidence in mammals of any such tonic contraction of the heart muscle. It would be in the highest degree unphysiological, since by resisting the inflow of blood into the heart it would be a hindrance to the circulation of the blood as a whole. So many different interpretations have been given of the expression *tone* of the heart that it would be better to avoid the word altogether.

SYSTOLIC OUTPUT OF THE HEART. The rate at which the blood circulates round the whole body depends on the quantity of blood which leaves the left heart per unit of time. The height of the arterial pressure also depends on the rate at which blood enters the arterial system. The determination of the output of the left ventricle is therefore one of the most important problems in physiology. The output of the right ventricle must be equal to that from the left ventricle, otherwise the blood would accumulate on one or other side of the heart and bring the circulation to a standstill. It must be remembered, however, that the coronary arteries, supplying the wall of the heart itself, leave the aorta at its very commencement, just beyond the semilunar valves. The quantity of blood passing per unit of time through the aorta is therefore less than that flowing through the pulmonary artery by the amount of blood which traverses the coronary vessels. The true output of each ventricle per minute is therefore given, not by the flow through the aorta, but only by the flow through the pulmonary artery (Anrep).

The methods which have been devised for determining the cardiac output fall into two classes. In the first class it is sought to determine the total volume of blood leaving the right or left ventricle in the course

of a given time, say one minute. If this amount be divided by the number of heart beats in the same time, the output of each ventricle per beat (stroke volume) is obtained. A second method consists in the determination of the volume changes in the ventricles at each beat of the heart. During diastole the ventricles are receiving blood, and increase in volume; during systole they expel blood, and therefore diminish in volume. The change in volume at each beat, therefore, gives the combined output of right and left ventricles, and must be divided by two in order to give the output of either ventricle separately.

METHODS OF DETERMINING OUTPUT

(i.) THE HEART-LUNG PREPARATION. In a method devised by Starling it is possible to determine the output of the left ventricle under all manner of conditions, and to

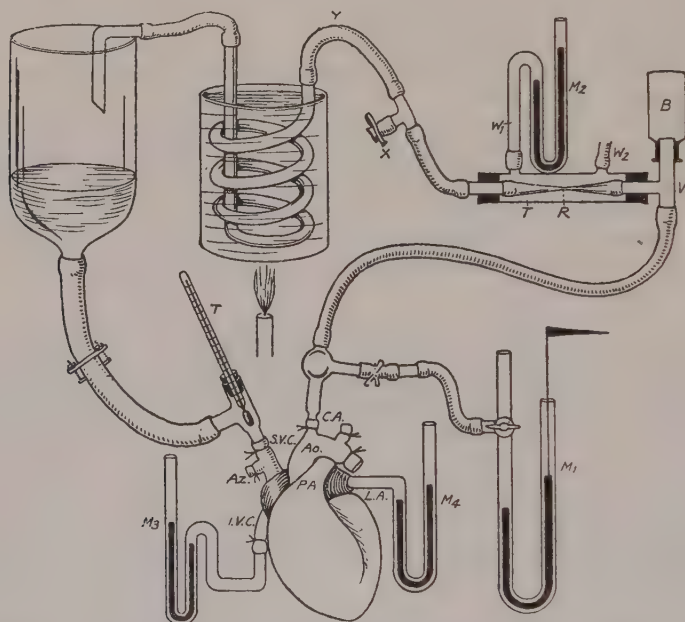


FIG. 382. Arrangement of Apparatus for Working on the Isolated Mammalian Heart. ('Heart-lung Preparation.')

The different parts are not drawn to scale, and the lungs are not shown. (STARLING.)

vary at will the systemic arterial resistance, the venous pressure, the filling of the heart, or the temperature of the blood supply to the heart. The arrangement of the apparatus is shown in Fig. 382. Artificial respiration being maintained, the chest is opened under an anæsthetic. The arteries coming from the arch of the aorta—in the dog, the brachio-cephalic and the left subclavian—are then ligatured, thus cutting off the whole blood supply to the brain, so that the anæsthetic can be discontinued. Cannulæ are placed in the brachio-cephalic artery and the superior vena cava. The cannulæ and the large venous reservoir are filled beforehand with defibrinated blood. The descending aorta is closed by a ligature. The only path left for the blood is by the ascending aorta and the cannula *CA* in the brachio-cephalic artery. The arterial cannula communicates by a T-tube with a mercurial manometer M^1 to record the mean arterial pressure, and passes to another T-tube *V*, one limb of which projects into a bottle *B*. The air in this vessel will be compressed with a rise of pressure and will serve as a driving force for the blood through the resistance. It thus takes the part of the resilient arterial wall. The other limb of the T-tube passes to the resistance *R*. This consists of a thin-walled rubber tube (*e.g.* a rubber finger-stall) which passes through a wide glass tube provided with two lateral tubulures *W*, *W*. One of these is connected with a mercurial manometer

M^2 and the other with an air reservoir into which air can be pumped. When air is injected into the outer tube, the tube R collapses, and will remain collapsed until the pressure

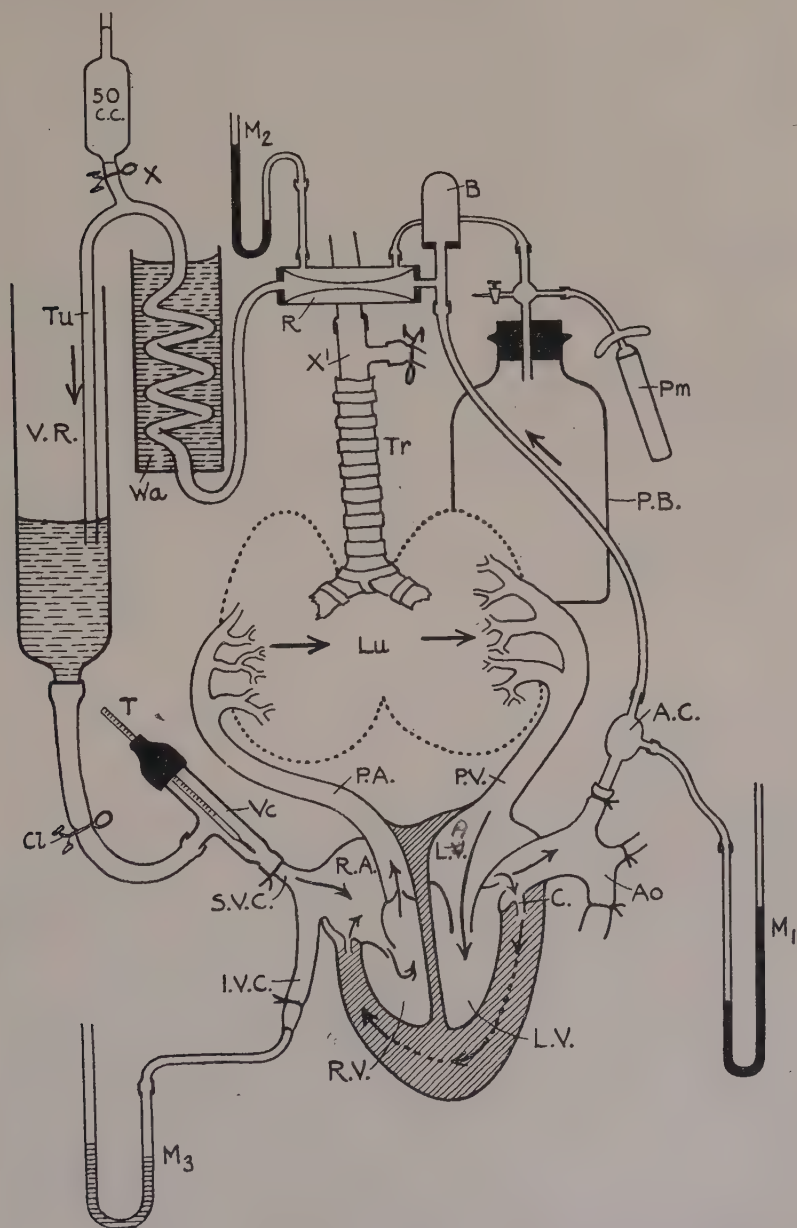


FIG. 383. Diagram of Circulation in Heart-Lung Preparation. P.B., Pressure bottle. Pm, Pump. Wa, Warming apparatus. V.R., Venous reservoir. Cl, Adjustable clamp. A.C., Arterial cannula. R.V., Right, and L.V., Left ventricle. C., Coronary supply. P.V., Pulmonary vein. Lu, Lungs. Tr, Trachea. X^1 , Tracheal tube. Other letters as in Fig. 382. Direction of blood flow indicated by arrows.

of the blood within it is equal or superior to the pressure in the air surrounding it. It is thus possible to vary at will the resistance to the outflow of the blood from the arterial side. From the peripheral end of R the blood passes at a low pressure through a spiral

immersed in warm water into a large glass reservoir. From the reservoir a wide india-rubber tube leads to a cannula, which is placed in the superior vena cava *SVC*, all the branches of which have been tied. This cannula is provided with a thermometer to show the temperature of the blood supplied to the heart. A tube placed in the inferior vena cava and connected with a water manometer shows the pressure in the right auricle. On the recording surface we thus have a record of the arterial pressure, and of the pressure within the right auricle. The output of the whole system can be measured at any time by opening the tube *X*, clamping *Y*, and allowing the blood to flow for a given number of seconds into a measure. The course of the circulation is shown in Fig. 383.

This method, although of considerable value in giving information as to the conditions which determine the output of the left ventricle and the maximum capacity of the heart as a pump, tells us nothing as to the output of the left ventricle under normal conditions in the intact animal. For this purpose some indirect means must be adopted which can be used on the intact animal and if possible on man himself. Moreover the output as measured on the other side of the artificial arterial resistance represents the ventricular output minus the blood flow through the coronary arteries. It is possible, however, to insert a cannula into the coronary sinus, and so to measure the blood flow through the heart muscle. The coronary circulation must be added to the flow through the arterial resistance in order to arrive at the correct total output of the left ventricle.

(ii.) APPLICATION OF THE FICK PRINCIPLE. If we know the difference between the oxygen content of the venous and arterial blood, it is clear that a determination of the oxygen intake by the lungs over a given interval of time will tell us how much blood has passed through the lungs during that time. This method has often been applied to intact animals, mixed venous blood being drawn from the right ventricle. Zuntz in one case found that in a horse weighing 360 kilos, 2733 c.c. of oxygen were taken up in the lungs per minute, while the arterial blood contained 10.33 per cent. more oxygen than the venous blood. Since every 100 c.c. of blood that passed through the lungs had taken up 10.33 c.c. of oxygen, and 2733 c.c. had been taken up in the course of a minute, it follows that

$$\frac{100 \times 2733}{10.33} = 26,457 \text{ c.c.}$$

of blood must have passed through the lungs in the time. This was the output of blood by the right ventricle in a minute and was equivalent to 0.00122 of the body weight per second. Instead of oxygen differences, CO_2 differences may be taken, and the total output of CO_2 by the lungs determined.

DETERMINATION OF CARDIAC OUTPUT IN MAN. Krogh has devised a method for determining the volume of blood flow through the lungs in a given time by finding out how much nitrous oxide is taken up from a mixture of nitrous oxide and air with which the lungs are filled. Knowing the composition of the alveolar air and the absorption coefficient of nitrous oxide in blood at the tension and temperature at which this gas is present in the pulmonary alveoli, and determining the amount of this gas which has disappeared from the mixture breathed during a certain number of seconds, it is possible to estimate the volume of blood which has passed through the lungs during the same time. Similar methods, employing other gases, have been used.

At present the methods in most general use for determining the minute output or minute volume of the heart are more closely similar to the original method of Zuntz, in that the volume of blood passing through the lungs is calculated from the output of CO_2 during a given time compared with the relative amounts of this gas in the arterial and venous bloods respectively. The only thing that is necessary is to find the volume of CO_2 in the arterial and venous blood of man without the operative procedures which were employed by Zuntz for animals. In Field's modification of Barcroft's and Haldane's methods, the tension of CO_2 in the arterial blood is obtained by determining the amount of this gas in ordinary alveolar air, since the alveolar tension of CO_2 is identical with the tension of this gas in the arterial blood. This tension must be converted into percentage content by obtaining a sample of blood and finding the amount of CO_2 it will take up at different tensions. The tension of CO_2 in the venous blood coming into the lungs by the pulmonary artery is given by a determination which is carried out as follows:—

The subject, having expired deeply, takes three deep breaths in succession of a mixture containing about 94 per cent. oxygen and 6 per cent. CO_2 , i.e. just above what is known to be the tension of this gas in arterial blood. The large amount of oxygen is supplied in order to prevent errors due to anoxæmia and consequent alteration in the CO_2 dissociation curve of the blood. These three breaths are taken within fifteen seconds.

As the total circulation time in a man at rest is about thirty seconds, there is no time for the blood which has taken up CO_2 from the lungs to come back to the lungs, *i.e.* equilibrium is established between the air in the alveoli and the continually renewed venous blood arriving at the alveoli by the pulmonary artery. After the third breath the alveolar air is collected. This is in equilibrium with the mixed venous blood, and the tension of CO_2 in the latter can be calculated from a determination of the percentage amount of CO_2 in the alveolar air. This is converted into percentage of CO_2 in the venous blood by reference to the CO_2 dissociation curve, as was done for arterial blood. In this way we find the difference between the CO_2 content of arterial and venous blood, *i.e.* of the blood leaving and of the blood entering the lungs. Before these determinations are carried out, the total CO_2 given off by the individual is measured by collecting his expired air for ten minutes in a Douglas bag. Of course the subject's condition must be uniform throughout the experiment. We thus obtain the same sort of figures as were obtained by Zuntz in his experiments on animals. Thus, if it were found that the difference in CO_2 content of arterial and venous blood was 4 c.c. per 100 c.c. blood, while the total amount of CO_2 given off from the lungs in the course of a minute was

200 c.c., the total amount of blood would be $\frac{200}{4} = 50$ times 100 c.c. = 5 litres, which

would thus be the 'minute' volume of the heart of the subject in question.

CARDIOMETRIC METHOD. Of the various methods which have been devised for recording plethysmographically the changes in the volume of the heart at each beat

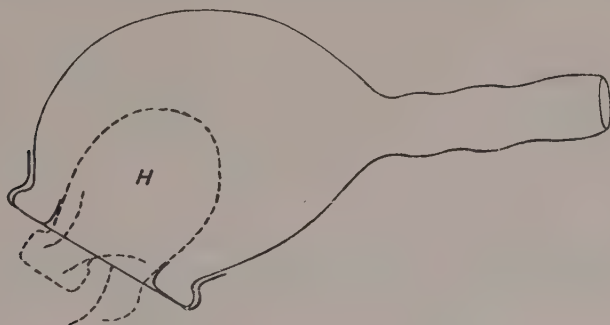


FIG. 384. Henderson's Glass Cardiometer.

the simplest is that devised by Henderson. The chest and pericardium being opened, a glass cardiometer, of the shape shown in Fig. 384, is slipped over the heart. This cardiometer consists of a glass sphere with a wide opening. To the margin of the opening is tied a rubber diaphragm with a hole in it, which accurately fits the heart as it lies in the auriculo-ventricular groove. The tube of the cardiometer is connected with some form of volume recorder. The disadvantage of this method is that the graphic record of rapid and ample changes in volume is one of the most difficult problems in experimental physiology, the inertia and friction of the moving piston tending to deform the shape of the curve obtained. It is possible, however, to obtain a piston recorder moving sufficiently freely to give a fairly correct reproduction of the volume changes of the heart, provided that these do not occur with too great rapidity. It has been suggested by Piper to convert the volume changes into small pressure changes, and to record these latter by one of the methods described above, and this method has been used by Katz and Wiggers.

FACTORS WHICH DETERMINE OUTPUT. The output of the left ventricle is best studied in the heart-lung preparation. It is self-evident that provided the venous inflow remains constant, the minute output, when considered over a reasonable interval of time, must also be constant and unaffected by considerable alterations of arterial resistance or heart rate. Thus, with a moderate venous inflow the output remains constant whether we maintain the average arterial pressure at 60 mm. Hg or at 160 mm. Hg. It is also unaffected by altering the rate of the heart from 80 beats per minute up to 160 or even 200 beats per minute. On the other

hand, the output must at once be altered by changes in the venous inflow and, as already stated, can be varied in a heart weighing 50 gms. from a few c.c. up to 3000 c.c. per minute. The only essential in this preparation is that the output from the left ventricle and the pressure in the aorta must be sufficient to maintain a circulation through the coronary vessels.

With increasing inflow of blood into the heart, the large veins, auricles and ventricles naturally become more filled during diastole; and during systole of the ventricles, when the auriculo-ventricular valves are closed, the blood rushing in from the venous system must accumulate in the big veins and auricles to a still greater extent. The venous pressure therefore rises, with increased venous inflow. In so far as venous pressure is an index of venous inflow, we may say that the output of the heart increases with the venous pressure, so long as the heart is functionally capable of dealing with the blood it receives during diastole. But although the ventricular output in the isolated heart is practically independent of the frequency of the heart beat, with a constant venous inflow the venous pressure tends to fall, with diminished diastolic volume, as the heart beat increases in rate. The optimum venous pressure is that which fills the ventricle during its diastole to the maximum extent to which it is able to respond. As the rate of the heart increases, the inflow of blood can also be increased without causing over-distension of the ventricles. The increase of heart rate is, therefore, in the intact animal, an important factor in enabling this organ to deal with the maximum amount of blood. Although increase of rate does not alter the output with constant venous inflow, it does increase the *maximum* amount of inflowing blood which the heart is able to expel. At the same time, the lowering of pressure in the great veins near the heart increases the fall of pressure from the extrathoracic to the intrathoracic veins, and so aids the venous inflow into the chest.

As might be expected, the alterations in the vigour of the circulation depend in the first instance on the venous circulation. The greater the volume of the blood that is brought up to the heart by the accessory factors of the circulation, the greater will be the output of this organ. The changes in rate and force of the heart which accompany its increased activity and increased output, *e.g.* during exercise, represent merely the means by which this organ is able to deal in the most advantageous manner with the increased inflow.

THE WORK OF THE HEART. The energy of the ventricular contraction is expended in two ways: first, in forcing a certain amount of blood into the already distended aorta against the resistance presented by the arterial blood pressure; and secondly, in imparting a certain velocity to the mass of blood so thrown out. Thus the energy of the muscular contraction is converted partly into potential energy in the form of increased distension of the arterial wall and partly into the kinetic energy represented by the momentum of the moving column of blood. The work done at each beat may be calculated from the formula:

$$W = QR + \frac{wV^2}{2g}$$

where *W* stands for work, *w* for the weight, and *Q* for the quantity (volume in c.c.) of blood expelled at each contraction; *R* is the average arterial resistance or pressure in terms of height of a column of blood, during the outflow of blood from the heart, and *V* is the mean velocity at which the blood is expelled. In this equation *QR* is the work done in overcoming the

resistance,* and $\frac{wV^2}{2g}$ is the energy expended in imparting a certain velocity to the blood.

If we take 60 c.c. as the average output of each ventricle, 100 mm. Hg as the average pressure at the beginning of the aorta, and 500 mm. per second as the velocity imparted to the blood thrown into the aorta, we can roughly calculate the work done by the human heart at each beat :—

$$QR = 60 \times 0.100 \text{ m.} \times 13.6 = 81.6 \text{ gram-metres,}$$

or roughly 80 gram-metres. On the other hand, the expression

$$\frac{wV^2}{2g} = \frac{60 \times (0.5)^2}{2 \times 9.8} = 0.7 \text{ gram-metres.}$$

It is evident that this latter factor is negligible, and that with small outputs we may regard the work of the heart as sufficiently expressed by the output multiplied by the average arterial blood pressure. Taking the average pressure in the pulmonary artery at 20 mm. Hg, the work of the right ventricle at each beat would amount to about 16 gram-metres, a total for the two ventricles of about 100 gram-metres per beat, which is equivalent to about 10,000 kilogram-metres in twenty-four hours for a man at rest.

During muscular work this figure would be largely increased. Not only does QR become much larger, but the velocity factor is no longer negligible, since the work done in imparting velocity to the blood increases as the cube of the output per minute. If we take, as an example, a maximum effort on the part of an athlete, we may assume an output per beat of 180 c.c. and a pulse rate of 180 per minute (an output per minute of 32.4 litres) and an average arterial pressure of 120 mm. Hg.

Then

$$QR = 180 \times 0.120 \times 13.6 = 294 \text{ gram-metres.}$$

To determine the velocity of output, we assume that 180 c.c. of blood are thrown out into the aorta during $\frac{1}{3}$ second. This gives a velocity of 2.3 metres per second, assuming a cross section of 625 mm.² at the root of the aorta. Therefore

$$\frac{wV^2}{2g} = \frac{180 \times (2.3)^2}{2 \times 9.8} = 49 \text{ gram-metres.}$$

The total work of both sides of the heart will be :

$$\begin{array}{l} 294 + 49 + 59 + 49 = 451 \text{ gram-metres per beat, or 81 kilogram-metres per} \\ \text{Left side.} \quad \text{Right side,} \quad \text{minute.} \end{array}$$

It will be noted that now the velocity-factor accounts for nearly one quarter of the total work. This rate of work could probably not be maintained for more than a few minutes.

It is important to remember that the strain or tension, which is thrown on the cardiac fibres and which resists their contraction, will be determined not only by the blood pressure which has to be overcome, but also by the size of the ventricle cavities. Since the pressure in a fluid acts in all directions, the tension caused by any given pressure on the walls of a spherical vessel will increase as the square of the radius of the

* Since the period of systolic output occupies not more than $\frac{1}{3}$ of the cardiac cycle, the mean velocity during expulsion must be $2\frac{2}{3}$ times greater than the mean aortic velocity :

the following general formula $W = \frac{7QR}{6} + \frac{w(VC)^2}{gE^2}$, (where V is the mean aortic velocity,

C the duration of the cardiac cycle and E the duration of period of expulsion) gives the work of both ventricles. The expression QR is also only approximately correct. Supposing the pressure in the aorta at the beginning of systole is 50 mm. Hg, and at the end of systole 150 mm., the work could not be deduced accurately from the average pressure, but would need a simple application of the integral calculus for its determination. The expression employed above deviates from the real value by at most 10 per cent., and is therefore sufficiently accurate for our purpose.

vessel, since the pressure on the whole surface = $P \times 4\pi r^2$, when P = the pressure on unit surface. Moreover in the case of the heart, with increasing distension, the wall becomes thinner and the number of muscle fibres in a given area fewer, so that the larger the heart the more strongly will each fibre have to contract in order to produce a given tension in the contained fluid. At the beginning of systole the distended heart must therefore contract more strongly than at the end of the systole, if it is to develop an endocardiac pressure sufficient to overcome that in the aorta.

FACTORS MODIFYING THE ACTIVITY OF CARDIAC MUSCLE

INFLUENCE OF TENSION AND DISTENSION. When we examine the behaviour of a heart isolated from the rest of the body, as for

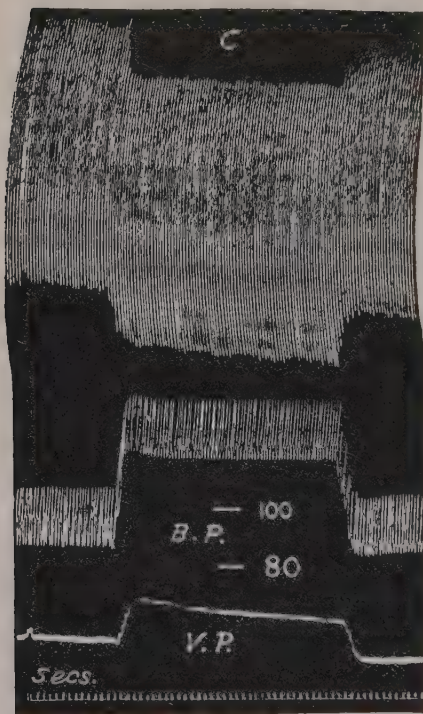


Fig. 385. Effect of Increased Arterial Pressure on the Volume Changes of the Heart, with a steady inflow of 154 c.c. Blood per 10 seconds.

C. = cardiometer curve. B.P. = arterial blood pressure. V.P. = pressure in the inferior vena cava. The lines 100 and 80 show the height of the blood pressure in mm. Hg.

instance in the heart-lung preparation, we find that it has a marvellous power of adaptation, *i.e.* of regulating its activity according to the mechanical demands which are made upon it. Thus, if we keep the venous inflow constant, it makes no difference to the output of the heart whether the average arterial pressure be maintained at 80 or 160 mm. Hg, although in the latter case the heart must do twice as much work in order to keep the outflow at the same level. Again, if we maintain the arterial pressure constant and alter the venous inflow, we find that within very wide limits the heart is able to expel against the arterial resistance the whole of the blood which flows into it from the veins. In this way we can alter the output of a small heart of 50 grammes from 300 to 3000 c.c. per minute. As we should expect, this variation in the work done by the heart is associated with corresponding variations in the chemical changes which occur at each heart beat. Evans has shown that the respiratory exchange of the heart increases *pari passu* with the work it has to do. Thus in an isolated dog's heart, weighing 70 grammes, with a constant output of 35 litres per hour, raising the arterial pressure from 80 mm. Hg to 140 mm. Hg increased the oxygen consumption from 228 to 404 c.c. per hour. In another experiment with a heart of 59 grammes, in which the arterial pressure was maintained constant at 80 mm. Hg, increasing the output from 9.3 to 92 litres per hour raised the oxygen consumption from 155 to 649 c.c. per hour. In these experiments the maximum efficiency of the heart, $\left(\frac{\text{work done}}{\text{energy expended}} \right)$, varied between 20 and 28 per cent., which is of the same order as that found for voluntary muscle. The remaining 70 to 80 per cent.

examine the behaviour of a heart isolated from the rest of the body, as for instance in the heart-lung preparation, we find that it has a marvellous power of adaptation, *i.e.* of regulating its activity according to the mechanical demands which are made upon it. Thus, if we keep the venous inflow constant, it makes no difference to the output of the heart whether the average arterial pressure be maintained at 80 or 160 mm. Hg, although in the latter case the heart must do twice as much work in order to keep the outflow at the same level. Again, if we maintain the arterial pressure constant and alter the venous inflow, we find that within very wide limits the heart is able to expel against the arterial resistance the whole of the blood which flows into it from the veins. In this way we can alter the output of a small heart of 50 grammes from 300 to 3000 c.c. per minute. As we should expect, this variation in the work done by the heart is associated with corresponding variations in the chemical changes which occur at each heart beat. Evans has shown that the respiratory exchange of the heart increases *pari passu* with the work it has to do. Thus in an isolated dog's heart, weighing 70 grammes, with a constant output of 35 litres per hour, raising the arterial pressure from 80 mm. Hg to 140 mm. Hg

of the energy is dissipated as heat. The efficiency of the performance of the heart is higher with heavy than with light work.

Careful investigation of the volume and pressure changes of the heart under varying conditions of arterial resistance and venous filling enables us to throw some light on the mechanism of this power of adaptation. Let us take first the changes in volume as recorded by the cardiometer, and suppose a heart is contracting 100 times per minute, forcing out at each beat 10 c.c. of blood into the aorta against an average pressure of 80 mm. Hg,

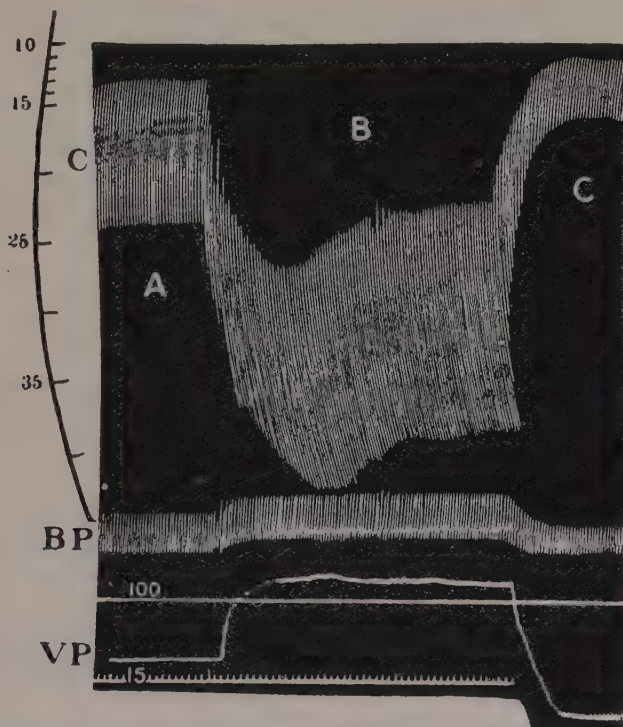


FIG. 386. Effect of Alterations in Venous Supply on Volume of Heart. Heart, 67 grms.

	Arterial pressure. mm. Hg.		Venous pressure. mm. H ₂ O.		Output of heart in 10 secs. c.c.
A . . .	124	=	95	=	86
B . . .	130	=	145	=	140
C . . .	124	=	55	=	33

The curved line at the side represents the value of the cardiometer excursions, *i.e.* of alterations of ventricular volumes, in cubic centimetres.

with systolic and diastolic pressures respectively of 100 and 60 mm. Hg. In order that the left ventricle may force 10 c.c. of blood against this resistance, the pressure in its interior must rise at each heart beat above the maximum systolic pressure in the aorta, *e.g.* to 110 mm. Hg. The aortic valves will open as soon as the pressure rises above 60 mm. Hg. Suppose the arterial resistance is now increased so as to bring the average pressure up to 120 mm. Hg. The heart now may raise the pressure in its interior to 120 mm. Hg. This will be higher than the diastolic pressure in the aorta and a certain amount of blood will escape, but the outflow of blood will cease as soon as the pressure in the aorta is equal to that in the ventricle. Diastole will then occur, the ventricle will relax before it has emptied out 10 c.c. of blood. Let us

assume it has forced out 3 c.c. of blood, so that the excess of 7 c.c. remains at the end of systole. Meanwhile, the venous inflow is proceeding at the same rate as before, so that at the end of diastole its diastolic volume will be increased by 7 c.c. At the next beat we find that the contraction of the ventricle is much more forcible. The maximum pressure now rises to 130 mm. Hg and 8 c.c. of blood are sent out into the aorta. At the end of this beat the heart will be still fuller than before, containing an excess of 9 c.c. of blood. The third beat is still more forcible, the intraventricular pressure rising to a maximum of 140 mm. Hg, and now 10 c.c. of blood are expelled. After this, the heart goes on beating regularly, expelling 10 c.c. of blood at each beat, *i.e.* the same amount as it receives from the veins. But the heart remains more dilated than it was previously, since it contains an excess of 9 c.c. of blood. If now the arterial resistance be suddenly reduced to its previous amount, the first beat after the change may send out 17 c.c. of blood, the second beat 12 c.c. of blood and the third beat 10 c.c. as before. We see, therefore, that an increased liberation

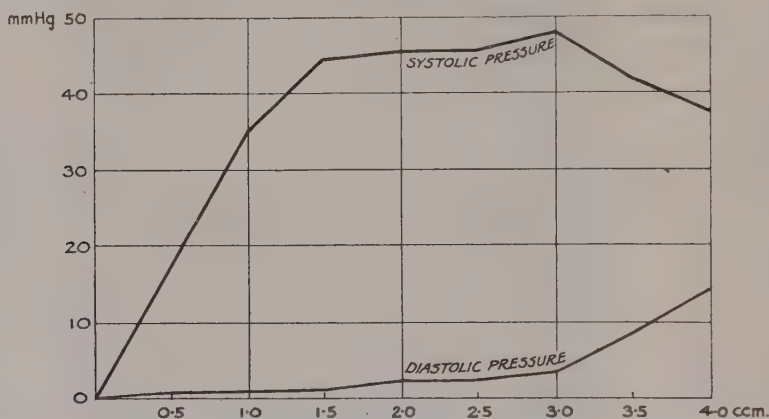


FIG. 387. Relation of the Tension developed during Isometric Contraction of the Tortoise Ventricle to the Filling (*i.e.*, initial length of fibres) of the Ventricle. (KOZAWA.)

of energy results from the contraction of the heart muscle when there is an increased diastolic volume of the heart and *vice versa*; but increased diastolic volume means greater length of the muscular fibres composing its wall, so we arrive at a statement that, as in voluntary muscles, the energy of contraction is a function of the length of the muscle fibres. This important generalisation is commonly called Starling's 'Law of the Heart.'

This reaction of the heart to increasing distension has long been known, but was ascribed to the excitatory influence of tension on the muscle fibres. In a resting heart increasing distension of its cavities will tend to stretch its muscle fibres and therefore to exert a tension on them. By accurately recording the pressure changes within the contracting ventricle under varying conditions, it has been found that the tension on the fibres is not the determining factor. In a heart beating regularly, the inflow of blood is proceeding during the relaxation of the ventricles, *i.e.* the muscles are giving before the inflowing blood. The latter is therefore able to distend the heart without exercising more than a minimum pressure on its walls. With a small inflow it is found that the pressure in the ventricles may be approximately zero at the end of diastole, whether the heart is contracting against a resistance of 80 mm. Hg or a resistance of 120 mm. Hg, or, with a moderate arterial resistance, whether it is receiving 5 c.c. or 10 c.c. during the period of diastole. With a still larger outflow or a bigger resistance there is an appreciable rise of tension within the ventricles at the end of diastole. But that the change in *dis-*

tension, i.e. in the diastolic length of the muscle fibres, is the chief factor in determining the energy of the subsequent contraction is evident on reference to Fig. 387, which shows the reaction of the tortoise ventricle contracting isometrically to increasing filling. It will be seen that as the diastolic filling increased from 0 to 1.5 c.c., the intraventricular pressure developed during systole increased from 0 to 45 mm. Hg. The maximum systolic pressure (48 mm. Hg) was developed with a filling of 3 c.c. and an initial tension within the heart of 3 mm. Hg. Further increasing the filling to 4 c.c. caused for the first time a considerable rise of initial tension to 13 mm. Hg, but the result was to *diminish* the tension developed during systole. This means that up to a certain optimum length, the energy of contraction increases with every increase in initial length of the fibres. Beyond this point it requires considerable tension to cause a further increase in length, but this is associated with a diminution in the effectiveness of the contractions.

The capacity of the heart for adapting itself to changes in mechanical demands made upon it will be limited by the inability of the heart to dilate further, as is probably the case in the intact animal, where its dilatation is limited by the pericardium, and by the mechanical disadvantage at which the further dilated heart acts. The greater its diastolic volume, and the more nearly globular its form, the greater the mechanical disadvantage of the muscle fibres in raising the pressure in the interior of the ventricles, so that by continually increasing the demands on the heart, we shall finally arrive at a stage at which this organ is unable to deal with the blood supplied to it and rapidly fails to expel any of its contents.

Evidence of a relation between heart volume and total energy consumption was furnished by the demonstration, by Evans and Matsuoka, that there is a parallel between heart volume and oxygen usage. Subsequently Anrep showed that in the isolated heart, within physiological limits, a given increase in the total *work* of the ventricle, whether brought about by augmented inflow or by a rise in the arterial resistance, is always accompanied by the same increase in the diastolic volume of the ventricles. Determinations of the oxygen usage of the heart by Visscher and Starling also show that, within limits, when the diastolic volume is the same, the oxygen usage is the same, whatever may be the amount of work done: in other words, the oxygen utilisation, the work done, and the diastolic volume are closely correlated, the first two being probably determined by the last, over rather wide ranges. Beyond the point of maximal performance this relation no doubt breaks down, diastolic volume and oxygen utilisation showing a further increase, but the work accomplished diminishing; this holds good in general whenever, with an increased volume in diastole, there is a reduced efficiency, as is the case when the heart fails.

The physiological condition of the heart is measured by the maximum pressure which it is able to produce in its cavities when it contracts, starting from a certain initial size or length of fibres. As the heart becomes fatigued this pressure falls, so that the heart must dilate in order that each contraction shall produce the same maximum pressure as before. Fatigue of the heart is shown therefore, not by failure to do its work, but by the fact that it can do its work only when it is undergoing considerable dilatation. Dilatation is therefore a measure of fatigue.

What is often spoken of as the 'tone of the heart' is really synonymous with physiological condition. A heart in good condition has a 'high tone.' It empties itself almost completely at each beat, even when receiving a considerable quantity of blood during diastole. A heart with a 'low tone' is in the condition of a fatigued heart. It is greatly dilated and when it has finished contracting still contains a large amount of residual blood.

This property of the cardiac muscle is responsible for the power of 'compensation' possessed by a diseased heart. We may take as an example the destruction of one aortic valve, a lesion which can be produced experimentally in a dog. In this case, immediately after the lesion is established, no additional resistance is offered to the expulsion of the blood, and the ven-

tricle will send the normal amount into the aorta. During the succeeding diastole the blood at a high pressure in the aorta will leak back into the ventricle through the damaged valve. The arterial pressure therefore falls rapidly, and the ventricle receives blood from two sides, *i.e.* by regurgitation through the aortic valves, and in the normal way from the auricles and veins. At the end of diastole the ventricle is therefore overfilled. Increased stretching of its fibres, however, has the effect of producing an increased contraction, and the heart, at its next systole, throws out not only the normal quantity of blood, but also that which it has received back from the aorta. The arterial system thus receives at each beat the normal quantity of blood *plus* the amount which leaks back into the ventricle after each systole; so that the amount of blood remaining in the aorta and available for passage on to the capillaries is the same as in the normal animal. On this account, after a lesion of the aortic valves has been established, the average of the arterial pressure remains the same as before, although the pulse pressure at each heart beat is increased in amplitude. The augmented output by the ventricles naturally involves increased work on the part of their muscular walls, which react in the same way as skeletal muscle does to increased work, *i.e.* by hypertrophy. The final effect, therefore, is a heart bigger than normal, with hypertrophied and thickened walls, but capable of maintaining an adequate circulation throughout all parts of the body; in other words, complete compensation has taken place.

INFLUENCE OF TEMPERATURE ON THE HEART. As in voluntary muscle, a rise of temperature quickens all the processes associated with the activity of the heart. Warming of the heart quickens the rhythm, and cold slows it. In the intact heart beating in normal sequence, the shortening of the contractions of the different cavities with rise of temperature may be ascribed to the quickening of the sinus rhythm. The changes, however, which are produced by warming or cooling the whole heart, *i.e.* the shortening of the contraction with rise of temperature and the lengthening of the contraction with fall of temperature, are more marked than when the rhythm is changed by direct excitation of the sino-auricular node itself. The increase of rhythm with temperature is almost proportional to the temperature, and over a limited range this proportionality may be linear. At 40° C. the isolated mammalian heart may beat four times as frequently as at 25° C. Warming the heart beyond 44° C. may cause stoppage of the heart or send it into fibrillation. The heart beat in the dog generally ceases between 13° and 19° C.

Similar effects are produced on conduction, both in the heart muscle itself and in the special conducting tissues. Thus, cooling of the heart leads to an increase in the A.V. interval.

The contraction of the cardiac muscle, whether auricular or ventricular, is affected by changes of temperature in the same way, a rise of temperature lessening the duration both of the contraction and of the refractory period.

As in skeletal muscle, the slow individual contraction of the heart at low temperatures is more efficient than the quick contraction at high temperatures, *i.e.* when the muscle contracts slowly and maintains the intraventricular tension for a long time, less energy is required for the expulsion of a certain volume of blood than at a higher temperature.

INFLUENCE OF THE COMPOSITION OF THE SURROUNDING MEDIUM ON THE HEART MUSCLE. The tissues of the heart, like all other cells of the body, require a definite osmotic environment, *i.e.* a certain molecular concentration of the fluid in which they are bathed. This is equivalent to a 0.65 per cent. sodium chloride solution for the frog's

heart, and to a 0.9 per cent. solution for the mammalian heart. As Ringer first showed, the nature of the salts employed for making up the normal solution is all-important to the heart muscle. Thus, a strip of muscle from the apex of the tortoise's ventricle does not, as a rule, beat spontaneously. If it be immersed in a 0.7 per cent. solution of sodium chloride, it begins to beat rhythmically, after a short latent period. The contractions soon reach a maximum and then gradually die away. Sodium chloride therefore acts as a stimulus to contraction, but is unable to maintain the beats for any considerable length of time. The strip of muscle ceases contracting in a condition of relaxation. On now adding to the solution a trace of calcium chloride or calcium sulphate, the contractions begin again (Fig. 388). The relaxations

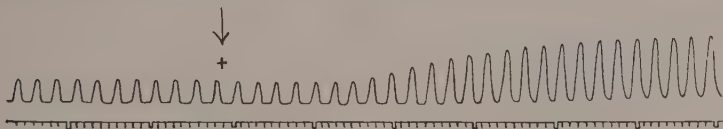


FIG. 388. Tracing of Contractions of a Frog's Heart, showing effect of adding a trace of CaCl_2 to the NaCl Solution used previously for Perfusion. (RINGER.)

The arrow marks the point at which the addition was made.

after each contraction then become more and more incomplete, until finally the heart stops in a tonically contracted condition. If now a trace of potassium chloride or phosphate be added, the contractions recommence and may last for many hours, although the solution contains nothing which can furnish energy to the contracting muscle (Fig. 389).

The exact significance of the different ions for the functions of cardiac and other forms of muscular tissue, though they have been the subject of many detailed investigations, must be still regarded as an open question.

The fluids, containing the three ions mentioned above in slightly varying proportions, are commonly used to maintain the beat in an excised heart either of a cold- or of a warm-blooded animal. In the case of the latter, it is necessary to keep the fluid warm, and saturated with oxygen. According

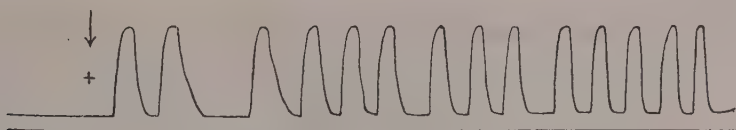


FIG. 389. A Frog's Heart, Poisoned by Excess of Calcium Salts, Recovers its Spontaneous Rhythm on adding a trace of KCl to the Perfusion Fluid. (RINGER.)

to Locke the addition of glucose to the solutions enables the beats to go on for a longer period of time, and will in fact renew the rhythm of a heart which has ceased beating while being fed with pure saline solution.

We have already discussed (p. 85) the composition of saline solutions suitable for the surviving heart or other tissues.

The influence of the chemical composition of the medium on the contraction of the heart may be investigated in the following ways:

One of the simplest methods of investigating the heart of cold-blooded animals is by perfusing the heart cavities with the fluid under investigation. Two forms of perfusion are made use of. In the method first introduced by Williams a double cannula is tied into the ventricle, the rest of the heart being cut away. The tubes leading to and away from the perfusion cannula are armed with valves so as to allow the fluid to pass only in one direction. The contractions of the ventricle may be recorded either by connecting the outgoing tube with a manometer, which may be a

mercurial or a membrane manometer, or by connecting some form of recording apparatus with the vessel in which the heart is contained, so as to register changes in the volume of the ventricle. A large number of different forms of apparatus have been devised for these purposes.

In another method, the fluid is allowed to flow through the whole heart, passing in by the sinus and out by the aortæ, or, as in Symes' method, in by a cannula tied in the auricle, and out by the aortæ (Fig. 390). It is usual to start with Ringer's fluid, and then to omit or increase the constituents one by one, in order to demonstrate their influence.

The heart of warm-blooded animals can also be investigated by a somewhat similar method. It was shown by Porter that the mammalian heart could be kept alive by transfusing oxygenated blood serum through the coronary vessels, and Locke found that the same results could be obtained by using warm oxygenated Ringer's solution, modified so as to have the same tonicity as mammalian blood. A simple apparatus for this purpose is that devised by J. A. Gunn, and shown in Fig. 391. It consists of an outer jacket, D, through which a constant stream of water at a little above body temperature is passed. The inner tube, F, is made of thin glass and at its lower end three small indentations, d, d, serve to support a thermometer, T, of such a thickness that only a small space is left between it and the inner tube. Into the lower end of the inner tube the cannula, C, is fixed by a rubber sleeve, while at the upper end a Y-shaped tube

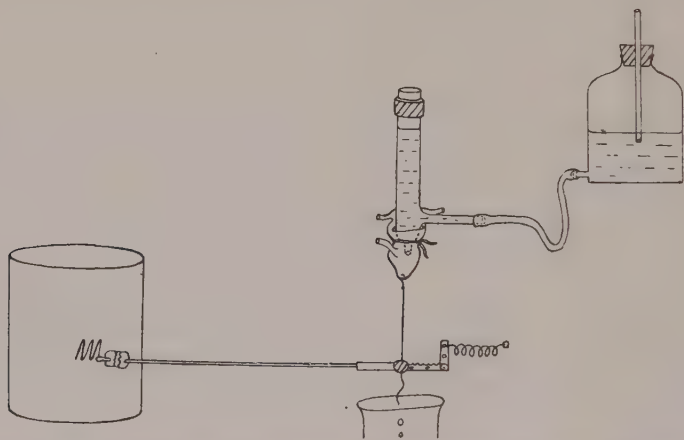


FIG. 390. Symes' Apparatus for Perfusion of Frog's Heart. (ANREP and HARRIS.)

delivers, either oxygenated Ringer's solution by B, or any other solution which is to be perfused by A. The proper perfusion pressure is provided by placing the reservoir of Ringer's, or other, solution at the desired height, and it is an advantage to have these reservoirs immersed in a bath kept at body temperature. In flowing through the narrow space around the thermometer, the solution is brought to the proper temperature. The water supply comes from a cold water tap, but on its passage to G passes through a metal spiral heated by a Bunsen burner. By varying the rate of flow and the position of the burner, the temperature of the water can be regulated with considerable accuracy. The heart having been excised and washed well in cold saline, so as to remove as much blood as possible, the cannula is tied into the aorta, and the perfusion started. The pressure of the fluid closes the aortic valves, so that the solution only passes into the coronary vessels. After passing through the heart, it reaches the right side, and flows away. A bent pin, to which a long thread is tied, is hooked into the apex of the heart, and the beats of the heart are recorded by means of a simple lever attached to the thread. The heart can be protected from drying by being surrounded by a wide tube which forms a moist chamber.

THE SIGNIFICANCE OF THE REACTION OF THE BLOOD FOR THE HEART BEAT. It was long ago shown by Gaskell that the reaction of the perfusing fluid has considerable influence on the frog's heart. When weak acids are transfused through this heart, the heart dilates, the

beats become smaller, slower, and finally disappear. A similar relaxation may be obtained as the result of the action of carbon dioxide. On perfusing with weak alkalis on the other hand, the relaxation during diastole becomes more and more incomplete, so that the heart is finally arrested in a contracted condition. There will thus be some reaction, intermediate between the weak acid and the weak alkaline fluids, which will represent the optimum reaction for the beat of the frog's heart. Mines has shown that this optimum reaction is not the same for the different cavities of the heart, nor for the hearts from various animals, a shifting of the reaction of the transfusing fluid to the acid side always bringing about a diminished contraction with dilatation, while the opposite effects are produced by an increase in the alkaline reaction. In the mammal under normal conditions, the chief variable factor affecting the reaction of the blood is the tension of carbon dioxide in this fluid; and any change in the carbon dioxide of the blood produces corresponding alterations in the heart's action. The effective factor is probably always the reaction or hydrogen ion concentration, so that a deficiency of CO_2 may be partially compensated for by an increased amount of lactic acid in the blood.

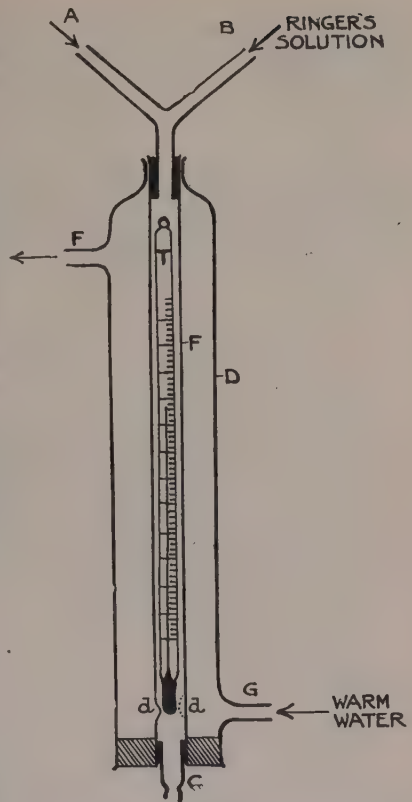


FIG. 391. Gunn's Perfusion Apparatus for the Mammalian Heart.

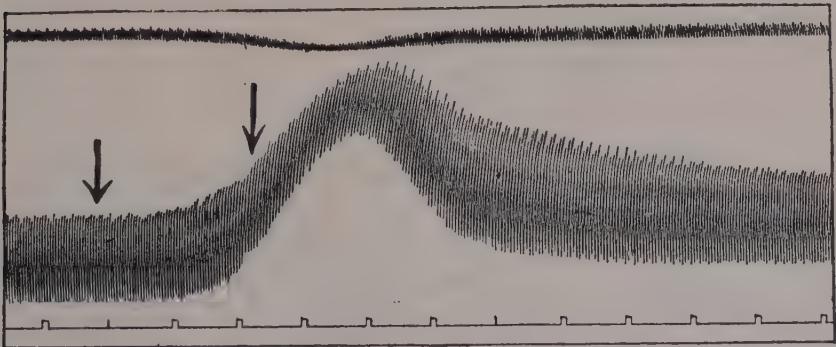


FIG. 392. Volume Curve of Ventricles (Cat) (lower curve).

The upper curve is the arterial pressure, maintained by an adjustable resistance at 130 mm. Hg. Between the arrows the air used for artificial respiration was replaced by a mixture containing 20 per cent. CO_2 and 25 per cent. oxygen. Note the dilatation with impaired contraction, followed by increased amplitude of contraction as the heart recovers and pumps out the blood accumulated in its cavities.

Increased pH causes (1) Slowing of the cardiac rhythm from its action on the sino-auricular node. (2) Slower propagation and deficient spread of the

excitatory wave through the auricular muscle and the A.V. bundle (Drury and Andrus). (3) Dilatation of the ventricles, which is greater than can be accounted for by the slowing of the heart and the greater filling thereby induced (cp. Fig. 392).

Yandell Henderson found that vigorous artificial ventilation of the lungs brought about a condition in which the heart's contraction was very forcible and the heart's cavities almost empty. He ascribed this condition to the hypertonicity of the heart muscle produced by washing the carbon dioxide out of the blood. The condition of low CO_2 content of the blood (and consequent raised pH) is known as 'acapnia.' Dale and

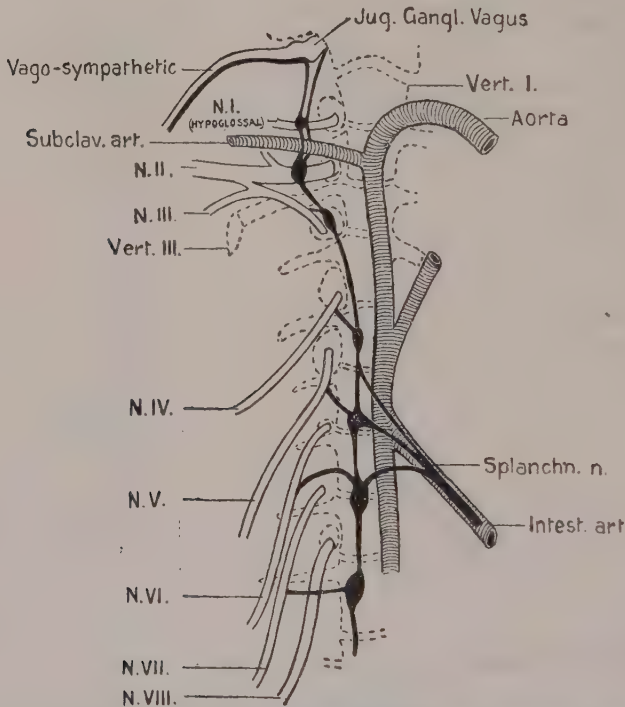


FIG. 393. Sympathetic Chain of Frog (right side) to show Connection with Vagus Nerve.

The sympathetic ganglia with their branches are black. Of the peripheral branches only the splanchnic nerve is represented. (Modified from ECKER.)

Evans have shown that, in the condition of acapnia there is paralysis of the spinal vaso-motor centres and a large fall of arterial pressure. The inflow of blood to the heart is therefore decreased and the heart, having only a small amount of blood to contract on, looks 'hypertonic,' *i.e.* reduced in size. The conditions may be at once removed by adding 5 per cent. CO_2 to the air used for the artificial ventilation. When the heart was perfused with a saline fluid of very alkaline reaction (pH 8.4) the coronary flow was so reduced, by constriction of the vessels, that the heart failed owing to oxygen lack. Up to pH 8.0 there was much less effect.

THE NERVOUS REGULATION OF THE HEART

In order that the activity of the heart may be adapted to the needs of the body as a whole, its automatic mechanism must be subject to the central

nervous system, which must be able to affect the heart in either of two ways, viz. by increasing or diminishing its activity. This subjection to the integrative action of the central nervous system is also necessary for the sake of the organ itself; otherwise the peripheral adaptation of the heart muscle to changes in arterial resistance might result in its exhaustion and permanent damage.

The regulation is effected through the intermediation of afferent and efferent nerve fibres connecting the heart with the central nervous system. The importance of these nerves is shown by the behaviour of animals in which they have been extirpated. Thus a dog, in which all the nerves of the heart had been divided, survived the operation for eight months, the pulse rate during the time not having appreciably altered and the animal being in a fair condition of health. Although he regained his normal weight after the operation, he was found incapable of carrying out even a moderate amount of work, such as that represented by running, since the mechanism for increasing the action of the heart in response to the needs of the muscles had been lost.

THE EFFERENT CARDIAC NERVES

The heart in vertebrates is supplied with nerve fibres from two sources: from the medulla oblongata along the vagus nerve, and from the upper dorsal region of the spinal cord through the mediation of the sympathetic system.

The fibres which run through the sympathetic system take a somewhat different course in the animals in which the regulation of the heart's activity has been chiefly studied, viz. the frog and the mammal. In the frog (Fig. 393) the sympathetic fibres leave the spinal cord by the anterior root of the third spinal nerve; they then pass through the *ramus communicans* to the corresponding sympathetic ganglion, whence they run up through the second ganglion and the annulus of Vieussens to the first ganglion; they then pass into the cervical sympathetic strand to the *ganglion trunci vagi*; here they join the vagus and pass down with the true vagus fibres to the heart.

In the dog, (Fig. 394) the sympathetic fibres leave the spinal cord by the anterior roots of the second and third dorsal nerves, run in the white rami communicantes to the stellate ganglion, and thence by the annulus of Vieussens to the inferior cervical ganglion. Cardiac branches convey the sympathetic fibres to the heart and, are given off from the stellate ganglion, the inferior cervical ganglion and the *ganglion trunci vagi*.

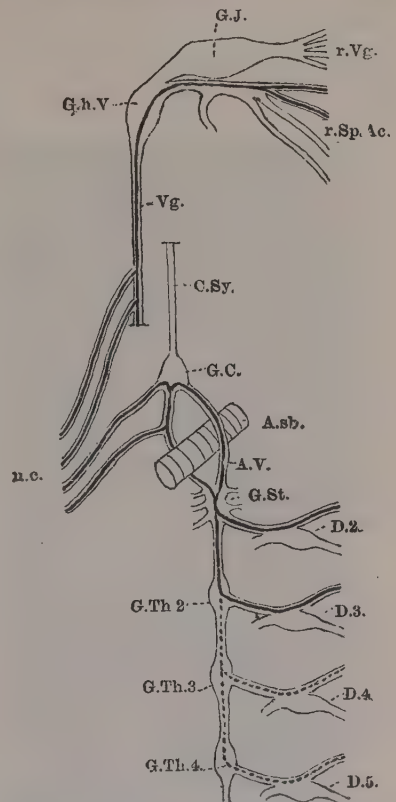


FIG. 394. Diagram of Cardiac Inhibitory and Accelerator Fibres in the Dog. (From FOSTER.)

- r.Vg. Roots of the vagus.
- r.Sp.Ac. Roots of the spinal accessory.
- G.J. Ganglion jugulare.
- G.h.V. Ganglion trunci vagi.
- Vg. Trunk of vagus nerve.
- C.Sy. Cervical sympathetic.
- G.C. Inferior cervical ganglion.
- A.V. Annulus of Vieussens.
- A.sb. Subclavian artery.
- n.c. Cardiac nerves.
- G.St. Ganglion stellatum.
- D.2, D.3, D.4, D.5. Second, third, fourth, and fifth dorsal spinal roots.
- G.Th. Ganglia of the thoracic chain.

By the nicotine method it is possible to trace out the cell connections of these fibres. As they leave the cord they are medullated nerve fibres, similar to the other fibres making up the visceral outflow throughout the dorsal region; the white fibres pass along the ramus communicans to the stellate ganglion, where they end, forming *synapses* with the cells of the ganglion. Here fresh relays of fibres, which are non-medullated, start and carry the impulses to the heart along the various cardiac nerves just mentioned. In the heart these fibres are distributed to the muscle fibres without the intervention of any other ganglion cells.

In the frog, the fibres which leave the vagus to pass to the heart make connection with the cells of Remak's ganglion, and probably with all the other intrinsic cardiac

ganglia described above, whence non-medullated fibres carry their impulses to the heart muscle. In the mammal, the right vagus arborises in the sino-auricular node, and the left nerve in the auriculo-ventricular node.

ACTION OF THE VAGUS.

The action of the vagus fibres on the heart is almost identical in frog and mammal and is exerted chiefly on the auricle. Since the auricle normally drives the ventricle, this also is affected. If in the dog the peripheral end of the cut vagus be stimulated, while the arterial blood pressure is being recorded by means of a mercurial manometer, the pulse is seen to become slower, or with a stronger stimulus to cease altogether, and the blood pressure falls towards zero. On discontinuing the stimulus, the heart begins to beat again and the pressure rises after a few beats to normal (Fig. 395).

If the stimulation of the vagus be prolonged, the blood pressure, on discontinuance of the stimulus, may rise above normal owing to the asphyxia of the vaso-motor centres produced by the prolonged cessation of the circulation. Even during the application of the stimulus the heart often begins to beat again with a slow rhythm. In this case we speak of an 'escape' of the heart from the vagus influence. This escape is generally confined to the ven-

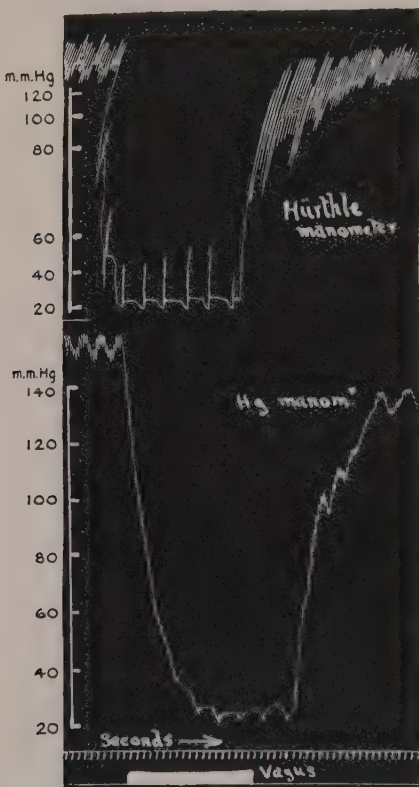


FIG. 395. Blood Pressure Tracing from Carotid of Dog (taken simultaneously with Hürthle's Manometer and Mercury Manometer), showing effect of Excitation of Vagus. (The Mercury Manometer gives very imperfect records of the pulsations during rapid changes of blood pressure.) (C. L. E.)

tricles, and, on opening the chest, the heart beats are found to be purely ventricular, the auricles and great veins remaining in a state of diastole. Vagus escape is favoured by distension of the heart cavities, and is often synchronous with the respiratory efforts which supervene after a certain duration of inhibition, as a result of the asphyxia of the respiratory centre.

When the arterial system is dilated, so that the mean systemic pressure and consequently the venous pressure during cardiac inhibition are low, or when the asphyxial gasps of the animal are prevented by anaesthesia or by a section of the spinal cord, the heart may fail to recover from the inhibition

produced even by a transitory stimulation of the vagus. In such cases it is necessary to knead the heart in order to restore its rhythmic action.

To study the influence of the vagus on the auricles and ventricles respectively, it is necessary to record separately the contractions of the different segments of the heart, or the electro-cardiogram may be used as an index to the changes in the rhythm, the origin of the rhythm, and the rate and direction of conduction in the heart under the action of nerve stimulation or section. The vagus may affect the heart in one of several ways. Its most marked action is on that part of the heart where it enters, viz. the venous end. The right vagus, since it connects with the sino-auricular node, has the greatest effect in lowering the rate. If its action is confined to the sino-auricular node, the sole effect of the vagus on the auricles and ventricles will consist in an alteration of rhythm. They may cease to beat altogether, or they may give beats of normal strength but at a slower rhythm than before. Often, indeed, under these conditions the beats of the ventricles may be increased in size, since the strength and extent of their contractions are determined by the length of their fibres, and this will be greater with any prolongation of the diastolic period, and consequent increased diastolic filling of the ventricle.

If the vagus (especially the left) acts on the auricles without affecting the sino-auricular node, the rhythm will be unaltered, but the response of the auricles will be diminished as regards the strength and duration of systole and the refractory period, and the amplitude of the excursions of the lever attached to them will therefore be considerably reduced, often to such an extent that they cause no movement of the lever. Under such circumstances the rhythm of the ventricles will be unchanged.

Generally the vagus absolutely stops the action of all parts of the auricles; in such cases the ventricles also cease beating. Very often after a short pause the ventricles commence to beat at a slow rhythm, and it is then seen that they are contracting independently of the auricles and sinus. That the ventricle is really inaugurating the beat is shown by the fact that occasionally one may observe a reversed beat, *i.e.* a contraction of the auricle following instead of preceding each ventricular contraction. Whether the vagus has a direct action on the mammalian ventricle is still doubtful; its effect is, at any rate, very slight as compared with that on the venous end of the heart. The fact that stimulation of the vagus, like division of the bundle of His, usually causes merely temporary cessation of the ventricular beat, would indicate that this nerve has its chief action on the auricles.

In the frog, it appears that the vagus has a direct inhibitory action on the ventricle, diminishing the strength of its contraction in response to the stimuli transmitted to it from the venous end. This action of the vagus on the ventricle is, however, not universal, and is not found in the tortoise. In both these animals the auricles show the same effects as in the mammal, viz. an influence limited to the rhythm when only the sinus is affected, or a diminution of the strength of contraction when the sinus is unaffected and the chief action of the vagus is on the auricular muscle.

Finally, the vagus may affect the conduction of the excitatory process from one cavity to another and to all parts of the ventricles. Under vagus stimulation the auricles may beat at a greater rhythm than the ventricles, a block having been produced in the tissue passing from auricles to ventricles, viz. the auriculo-ventricular bundle.

It is evident that these various effects are chiefly due to differences in the place affected.

Thus, if the vagus fibres which are distributed to the remains of the sinus are specially active, we shall get alterations of rhythm affecting the whole heart. If those which supply the A.V. bundle are excited, the most pronounced effect will be on the propagation of the excitatory process from auricles to ventricles.

Ever since the discovery in 1845 by the brothers E. H. and E. F. Weber of the action of the vagus on the heart, much work has been expended with a view to determine the intimate nature of the inhibitory process. Many facts point to the inhibitory impulses acting on the heart muscle itself. Thus, tetanisation of any portion of the frog's ventricle, especially if it be filled with blood, causes an evident relaxation of the part between the electrodes. Application of nicotine to the heart prevents stimulation of the trunk of the vagus from having any influence on the heart, presumably from paralysis of the cells of Remak's ganglion, which lie at the termination of the vagus fibres, or of the synapses between the vagus fibres and the ganglion cells. It is still possible to inhibit the heart by direct stimulation either of the fibres leaving this ganglion in the sino-auricular junction, or of the nerve trunks which run in the inter-auricular septum. We must conclude that the inhibition of the heart muscle is peripheral and depends on the direct action of the nerve fibres on the muscle cells themselves. These nerve fibres are paralysed by atropine, after administration of which no inhibitory effects can be produced by stimulation of nerve or muscle or any part of the heart. On the other hand, muscarine or acetyl choline apparently either stimulates the inhibitory nerve endings or else produces the same effect as the stimulation of these, and when applied to the isolated auricle or ventricle causes weakening of the beat and finally complete inhibition, an effect which can be removed by its antagonist atropine.

Two views have been held as to the essential nature of the inhibitory process. According to that put forward by Claude Bernard, the natural tendency of any tissue during rest is towards anabolism. Activity involves catabolism or breaking down of the living material, and this disintegration must be succeeded by a process of building up or anabolism, which restores the tissue to its previous functional condition. On this view the state of inhibition would merely prolong the period of rest intervening between two periods of activity, so allowing a greater time for restitution to take place. According to Hering and Gaskell anabolism as well as breakdown can be accelerated in a tissue. Excitation of the vagus nerve not merely allows the normal process of building up, which goes on during rest, to take place, but actually hastens this process.

If stimulation of an inhibitory nerve induces the opposite chemical change to that occurring during activity, one would expect to find that, just as an active part of a tissue is electrically negative to an inactive part, so a part of the tissue which is under the influence of an inhibitory stimulus should be *electro-positive* to any part which is not being so stimulated. According to Gaskell, this condition is realised in the heart of the tortoise. Doubt still exists, however, as to the exact interpretation to be put on this experiment.

Of recent years a direct chemical explanation has been more in favour. If potassium salts be present in a sufficient concentration in the circulating fluid, the heart is brought to a standstill in a condition of diastole, as if the vagus mechanism were in action. On removal of the excess of K ions, the heart at once starts beating again. Howell has claimed that during stimulation of the vagus, the amount of potassium in a diffusible form in the heart muscle is increased. He has therefore suggested that the action of the vagus in stopping the heart is due to the liberation of potassium salts. Potassium normally exists in a large percentage in the heart muscle, but in a combined form; and Howell assumes that stimulation of the vagus effects a dissociation of this combined potassium, so that the liberated ions are able to exert their inhibitory influence on the heart. According to Loewi, the vagus acts by producing some chemical substance, which is not potassium, but which has the power of depressing the activity of the different parts of the heart. If a frog's heart containing saline fluid be brought to a standstill, or its beats weakened several times in succession by stimulation of the vagus, the fluid can be removed by a pipette, and on introduction into a fresh heart will produce on the

latter the same effect as if the vagus nerve to the second heart were stimulated. It is possible that this substance may be acetyl choline, and that the effect of vagus excitation is to produce or liberate this substance in the immediate vicinity of the vagus endings.

THE TONIC ACTION OF THE VAGUS. If both vagi of a mammal be divided, or if a small dose of atropine be given, the heart as a rule beats more frequently, showing that, under normal circumstances, tonic impulses are constantly descending the vagi and holding the heart's action in check. The extent of the quickening which is produced by section of the vagi varies in different animals and is associated with the conditions of life of the animal and its powers of carrying out prolonged muscular exertions. Thus, in the dog or horse the pulse, which is normally slow, may be doubled in frequency by section of the vagi. In the rabbit, which has a frequent pulse and is able to run only for a short distance, division of both vagi causes very little alteration in the pulse rate. It is stated that the tonic action of the vagi is much greater in the hare than in the rabbit.

This tonic action may be increased by various conditions of the blood, *e.g.* the presence of drugs such as morphia. Central inhibition by way of the

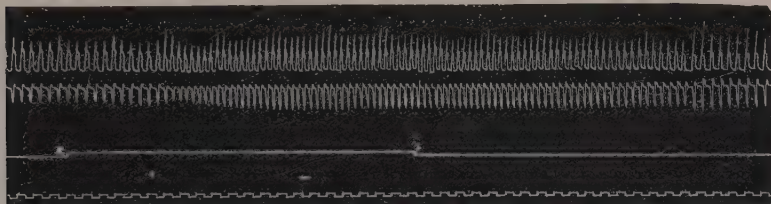


FIG. 396. Tracings of Ventricular (upper curve) and Auricular Contractions (lower curve).

From *x* to *y* the accelerator nerves were stimulated. Lowest line = seconds.

vagus may also be induced by a rise of blood pressure in the medulla, by increased intracranial pressure, or as a result of asphyxia.

ACTION OF THE SYMPATHETIC CARDIAC NERVES. Stimulation of the sympathetic cardiac nerves at any part of their course has an effect on the heart the exact reverse of that produced by stimulating the vagi. In most cases the pulse frequency is increased in consequence of the action of these nerves on the 'pace-maker' of the heart. The frequency attained by maximal stimulation of the accelerator nerves is independent of the previous rate of the heart beat. The increase in rate involves a shortening of the time of the cardiac cycle, which chiefly affects the diastolic period. The size of the auricular and ventricular contractions may be increased at the same time as their rate. In fact, like the vagus nerves, the sympathetic fibres of the heart can influence rhythm, strength of contraction, or conduction from auricle to ventricle, according to the part of the heart muscle which is affected.

The augmentor effect on the strength of the ventricular beats is often very marked. The sympathetic fibres are much less easily tired than the vagus fibres, and have a longer latent period. Whereas the latent period of the vagus in the mammal is considerably less than one second, that of the accelerator nerves may amount to ten or even twenty seconds (Fig. 396). Hence, if the vago-sympathetic of the frog be stimulated, the first effect is inhibition due to vagus action. The vagus nerve endings then become fatigued, and the influence of the accelerator fibres makes itself apparent;

the heart commences to beat, and the beats become more rapid and forcible than before (Figs. 397, 398).

Like the vagus, the sympathetic nerve fibres appear to exercise a tonic influence on the heart so that, after extirpation of the stellate ganglion on each side, the pulse may become permanently slowed.

THE ACTION OF ADRENALINE ON THE HEART. The medullary part of the suprarenal glands forms and, under certain conditions, secretes into the

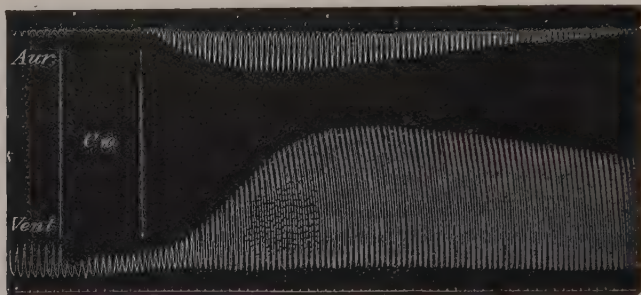


FIG. 397. Tracing to show Effect of Stimulation of the Vago-Sympathetic Nerve on the Frog's Heart. (GASKELL.)

The rhythm is unaltered, but the beats of auricle and ventricle are much decreased in size. On ceasing the stimulation the beats become augmented.

blood stream a substance, adrenaline, which has a marked action both on the heart and blood vessels and plays an important part in the regulation of the circulation. The action of adrenaline on any part of the body is practically identical with that of excitation of the sympathetic nerve supply to the same part. Indeed, it has been suggested that the action of the sympathetic nerves is actually due to the liberation of small amounts of this substance at the nerve endings, so that a local effect is produced. Its isolated action on the heart is best studied on the perfused heart or in the heart-lung pre-

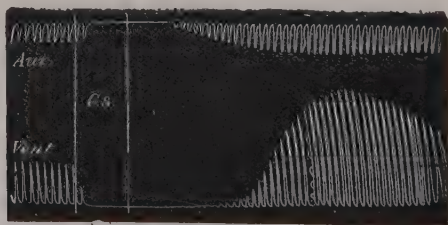


FIG. 398. A Tracing similar to Fig. 397. (GASKELL.)

In this case, however, the stimulation caused complete stoppage (inhibition) of both auricular and ventricular beats.

paration. On adding $\frac{1}{10}$ mgm. of this substance to the 500 c.c. of blood circulating through the heart-lung preparation, a maximum effect is at once produced and this lasts for 15 to 20 minutes. The action is, like that of the sympathetic nerve, accelerator and augmentor. Through its influence on the sinus or the sino-auricular node, the rhythm of the heart is markedly increased, in the dog to about 240 per minute. At the same time the energy of each contraction is augmented. This is especially shown in a heart which is beginning to fail and is therefore undergoing a certain degree of dilatation. Directly the adrenaline reaches the heart, the contractions become extremely energetic so that the heart rapidly diminishes in volume, the venous pressure

falls, and the blood flowing into it at each diastole is thrown out with violence into the aorta. The more powerful beat enables the output of the heart at each beat to be maintained or even increased, in spite of the shorter duration of the systole. With each beat the maximum pressure in the ventricle therefore rises to a marked extent (*see* Fig. 399). The stimulating effect of adrenaline is shown, moreover, by the fact that the oxygen intake is increased two or three times above that which obtained before the administration of the adrenaline. The action of adrenaline, therefore, is in general to enable the heart to cope with a bigger strain, either in the shape of arterial resistance or increased venous inflow, than it could do without the stimulus of this substance.

The wonderful adaptation of the heart to its functions is illustrated moreover by the fact that adrenaline, which increases the metabolism of the heart to such an extent, exercises at the same time a dilator effect on

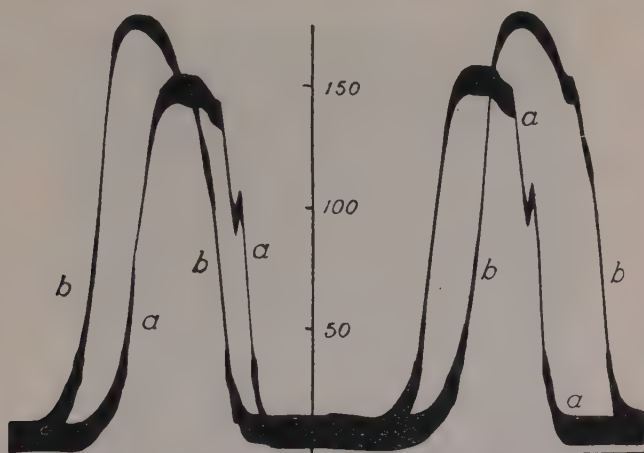


FIG. 399. Intraventricular Pressure Tracings (Left Ventricle) from Dog's Heart (Heart-lung Preparation). (S. W. PATTERSON.)

(To be read from right to left.) The scale shows pressure in mm. Hg.

a. Under influence of adrenaline.

b. Under simultaneous influence of adrenaline and CO_2 (15 per cent.).

the coronary vessels, so that the vessels are dilated by the action of the same hormone which evokes the need for an increased flow of blood through the working muscle.

There is a marked antagonism in the influence on the heart of the two hormones produced during general muscular activity. Carbonic acid in excess causes dilatation of the heart, diminished functional activity and slowing of rhythm. Adrenaline causes increased functional activity, diminution of cardiac volume and increased rhythm. The action of adrenaline is so pronounced that it is possible to administer 20 or 30 per cent. carbonic acid to a heart-lung preparation without altering its output, if adrenaline be administered at the same time. The heart is slowed by the carbonic acid, but the beat is maintained and contraction is effective in emptying the heart of its content.

THE HEART REFLEXES

The part of the nervous system chiefly concerned in the central co-ordination of the various afferent impulses which act on the heart is the

medulla oblongata. Here, in the dorsal nucleus of the vagus, we find the nerve cells giving origin to the efferent fibres of the vagus nerves, and also the collection of grey matter in which the afferent fibres of the vagus terminate. Direct stimulation of the vagus centre may cause slowing and stoppage of the heart. The tonic influence of the vagi is abolished by destruction of this centre. In this region we also find the vaso-motor centre, so that the activity of one can affect that of the other. This cardiac centre may be played upon by impulses arriving at it through various afferent nerves or from the higher parts of the brain and giving rise to the changes of the pulse rate associated with the emotional conditions, or it may be directly affected by the composition of the blood circulating through its capillaries.

The nerve cells, which give off the accelerator or augmentor fibres, are situated in the intermedio-lateral tract of the spinal cord, near the point of origin of these fibres. We might, therefore, speak of an augmentor centre in

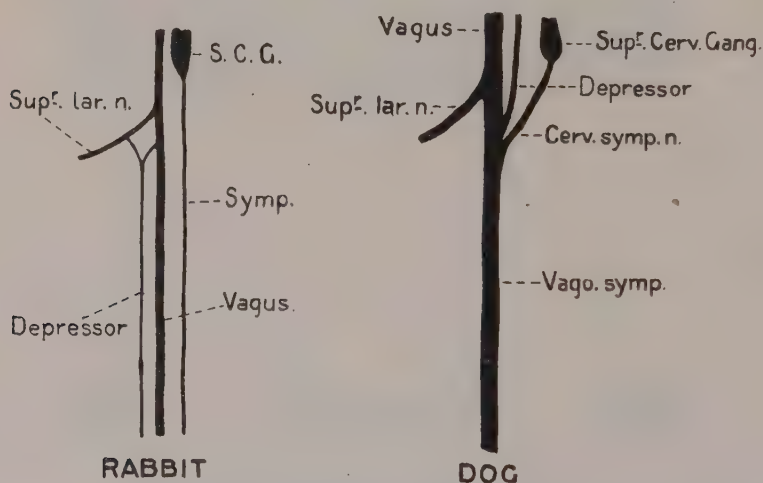


FIG. 400. Diagrams of the Connections of the Depressor Nerve in the Rabbit and Dog, according to Cyon.

It will be noticed that in the latter animal the depressor nerve runs in the vagus trunk, together with the sympathetic nerve, for the greater part of its course.

this region; but it seems probable that the activity of these cells is subordinate to impulses arriving at them from the common meeting-place of visceral impulses, viz. the medulla.

The most important of the afferent nerves, which affect reflexly the action of the heart, are the nerves coming from the heart itself and the aorta. In the mammalian ventricle, nerve fibres can be seen running over the surface of the ventricle; these are entirely afferent, stimulation of their peripheral ends causing no effect on the heart beat. Stimulation of their central ends may cause one of five conditions:

- (a) Slowing of the heart.
- (b) Acceleration of the heart.
- (c) Rise of blood pressure from constriction of the splanchnic area.
- (d) Fall of blood pressure by dilatation of the arterioles of the body.
- (e) Reflex movements.

The heart does not seem to be provided with the nerves of ordinary or tactile sensibility. There is no doubt, however, that under abnormal circumstances impulses arising in the heart can give rise to sensations of pain,

which are referred not so much to the heart as to the surface of the body over the left side of the chest and left arm, in the region of the distribution of the cutaneous branches of the second and third dorsal roots.

An important afferent nerve coming from the heart, or rather from the beginning of the aorta, is the *depressor nerve*. In the rabbit this arises by two roots, one from the trunk and the other from the superior laryngeal branch of the vagus, and runs parallel with the vagus to the cardiac plexus (Fig. 400). It is purely afferent, stimulation of its peripheral end causing no effect. In many animals the depressor fibres are bound up with the trunk of the vagus and cannot be excited separately. On stimulating its central end, fall of blood pressure (Figs. 401 and 445) and reflex slowing of the heart are produced, the latter effect being abolished by section of both vagi. It has been shown by Bayliss that the depressor effect is due to universal dilatation of the blood vessels of the body, chiefly in the splanchnic area. This nerve is

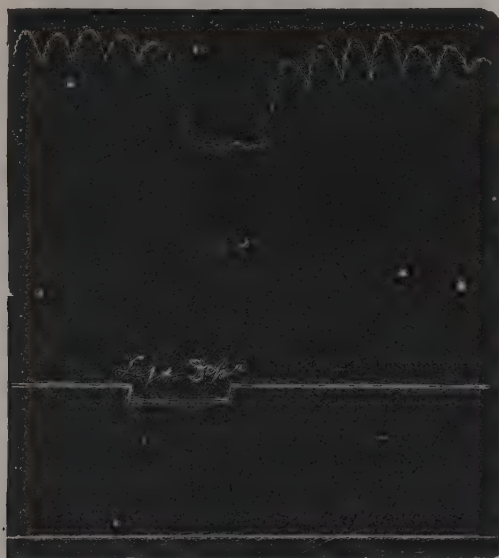


FIG. 401. Blood Pressure Curve from Rabbit, showing effect of Excitation of Central End of Depressor Nerve (Mercurial Manometer). (BAYLISS.)

brought into action by stretching or dilating the aorta, as happens when the blood pressure is high. It is stated that under these conditions a current of action may be detected in the trunk of the depressor nerve and that, if both depressor nerves be cut when the aortic pressure is high, the blood pressure rises still higher. We have here a means by which the heart can be relieved of a load too great for its powers.

Stimulation of the central end of the vagus generally causes reflex slowing of the heart through the cardiac centre and the other vagus. Inflation of the lungs may cause acceleration of the heart—whether due to diminution of the tonic action of the vagi, or to reflex excitation of the accelerator nerves, or to both causes, is not known. Most sensory nerves of the body when stimulated give either a slowing or a quickening of the heart. Stimulation of the fifth nerve, as in the nasal mucous membrane, always causes reflex inhibition.

There are two very important reflex mechanisms associated with the heart itself. If the arterial pressure be raised the heart is slowed in accor-

dance with Marey's law that *the pulse rate varies inversely as the arterial pressure*, while if the venous pressure is raised the heart is accelerated. This is accomplished by two mechanisms, balanced the one against the other, one actuated from the arterial, the other from the venous, side.

The first of these mechanisms is a result of reflex cardiac inhibition, in which afferent fibres of the depressor and vagus (chiefly the left) are excited by undue stretching of the arch of the aorta when the blood pressure rises. As a result of this the cardio-inhibitory centre is excited, with the sequel that efferent cardio-inhibitory impulses *via* the vagi bring about a reduction of the pulse rate.

Recent work by Anrep and Segall seems to necessitate some modification

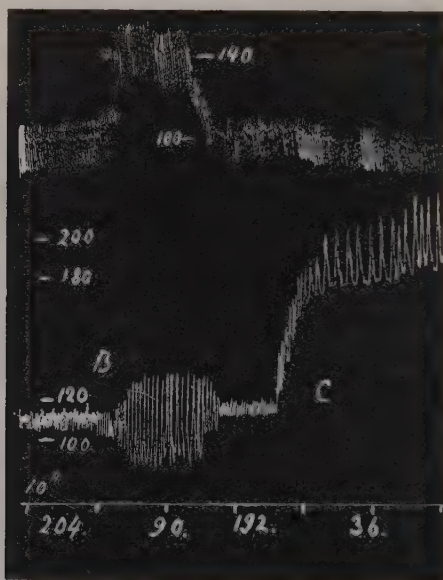


FIG. 402. Blood Pressure Tracings from a Dog in which the Circulation through the Head and Neck was maintained by a separate Heart-Lung Preparation.

The figures on the blood pressure tracings indicate pressure levels. Those beneath the time tracing show the pulse rates in the systemic circulation.

Upper tracing, arterial blood pressure in head. Lower tracing, blood pressure in aorta, vagi intact. At B the pressure was raised in the head circulation only, and at C in the aorta only. In both cases the heart (lower tracing) was inhibited. (ANREP and SEGALL.)

of this view of Marey's law. Their experiments were carried out with an adaptation of the heart-lung circulation by means of which the brain of an animal could be separately fed with blood while the animal's own heart supplied only its trunk and limbs. The advantage of this arrangement was that the blood pressure in the brain was under independent control, and quite unaffected by any systemic pressure changes due to alterations in the animal's own heart. The nervous connections between the brain and the heart of the same animal were undisturbed. It was thus possible to study separately the effects of alteration of pressure in the brain, as well as the cardiac reflexes. It was found that when the pressure in the brain was raised the heart was slowed if the vagi were intact, but not if they were divided (Fig. 402); rise of blood pressure in the animal's own aorta also caused a reflex slowing in the rate of its heart-beat when the vagi were intact.

The slowing expressed by Marey's law, therefore, would seem to be explicable, not only by reflex through the fibres of the depressor and vagus, as has been commonly supposed, but also by the direct effect of the raised arterial pressure in the vessels of the head.

Which structures in the head are affected by rise of pressure is the subject of dispute. Hering, and also Heymans, believe it to be the nerves of the *sinus caroticus*, i.e. the region where the common carotid artery bifurcates; the nerves in this region they believe to behave somewhat after the fashion of the depressor fibres in the aorta, so that when the sinus is distended, there is reflex cardiac inhibition (accompanied by reflex fall of blood pressure due to vasodilatation). Anrep and Starling believed the rise of pressure also to act directly on the cardio-inhibitory centre.

(Incidentally it should be stated that Anrep and Starling found that they could confirm the current belief in vaso-dilator reflexes, *via* the depressor nerve, as a result of increased aortic pressure.)

The other mechanism is a reflex, often called the Bainbridge reflex, which is started from either auricle and from the great veins, when these become distended by rise of venous pressure (Sassa and Miyazaki). Afferent impulses from the auricles travel up by the vagi (perhaps chiefly by the right one) and bring about reflex cardiac acceleration by (a) reducing the tone of the cardio-inhibitory mechanism (the principal factor), and possibly also (b) throwing the cardio-accelerator mechanism into action.

Anrep and Segall, by the use of the preparation referred to above, were able further to confirm the existence of this reflex from the right side of the heart. The mechanism of pulse rate regulation is diagrammatically illustrated in Fig. 403.

THE PULSE RATE IN MAN. The normal pulse rate in man is about 72 per minute. It is largely influenced by bodily movements, and varies considerably with age. The following Table represents the average pulse rate in man at different ages :

Age in years		Pulse rate per minute
0	..	136
5	..	88
10-15	..	78
15-60	..	68-72

It must be remembered that marked differences in the pulse rate may be found in different individuals without having any pathological significance. Thus pulse rates of 30 per minute and 120 per minute have been observed in men who were otherwise perfectly healthy. The pulse rate is raised by

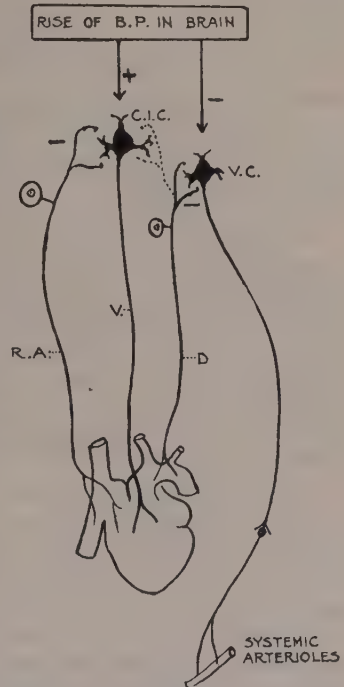


FIG. 403. Diagram to illustrate regulation of the pulse rate. D = depressor fibres, which reflexly increase the tone of the cardio-inhibitory centre. R.A. = afferent fibres in vagus from right side of heart which reflexly diminish the tone of the cardio-inhibitory centre. C.I.C. = cardio-inhibitory centre. V = efferent cardio-inhibitory fibres of vagus. V.C. = Vaso-constrictor centre, reflexly inhibited by rise of aortic pressure.

Rise of intracranial blood pressure excites the cardio-inhibitory centre and depresses the vaso-constrictor centre.

warmth and diminished by cold applied to the surface of the skin. It is also increased somewhat by the taking of food. The act of swallowing causes a reflex quickening of the rate by inhibition of the tonic vagus action.

THE CORONARY CIRCULATION

In the frog's heart, the spongy ventricular wall permits the access of blood between the fibres. In the mammalian heart, the muscular tissue is nourished through the coronary arteries, which break up into a meshwork of capillaries around all the fibres.

The flow of blood through the coronary circulation may be measured by introducing a cannula through the wall of the right auricle into the coronary sinus and collecting the blood from the latter outside the body. Another method is to feed a second heart, through the coronary arteries, with blood from the aorta and collect the total outflow from the cut pulmonary artery. By a comparison of these two methods, it is found, in the dog, that the flow through the coronary sinus forms about three-fifths of the total blood passing through the coronary arteries. It is therefore possible to measure the flow through the coronary sinus in the heart-lung preparation under varying conditions, and, by multiplying the figures so obtained by $\frac{5}{3}$, to obtain the approximate total flow through the coronary circulation.

The energy of the heart is probably derived, like that of skeletal muscle, from the breakdown of glycogen, and since no resting periods other than those of diastole are ever possible, recovery must be complete in that short period. That the actual contraction, like that of skeletal muscle, is probably anaerobic is shown by the fact that the heart will continue to beat for a minute or two after oxidations have been almost abolished by hydrocyanic acid. Such an anaerobic process involves the accumulation of lactic acid. Since the efficiency of the heart is ultimately dependent on an adequate supply of oxygen, the importance of the coronary blood flow is evident. The amount of blood passing through it per gramme of heart per minute may under extreme conditions rise to as much as 5 c.c.

Other factors remaining the same, the coronary flow depends primarily on the mean pressure at which the coronary arteries are supplied, whether the work of the heart is varied or not. The great effect of general arterial pressure on the coronary flow is shown in the following Table :—

Heart weight, 107 grammes. Total Systemic output per minute, 1400 c.c.

Arterial pressure	Coronary circulation per minute
60	50
100	90
128	124
166	208
190	500

But this circulation must also be adapted to the amount of work that the heart is doing, since the oxygen usage of the heart increases with the amount of work it is given to do. When we investigate the coronary flow in the isolated mammalian heart, as in the heart-lung preparation, we find, accordingly, that it is increased whenever an increase is demanded to supply the necessary oxygen. Hence we find that :—

(a) Reduction in the oxygen saturation of the blood passing through the heart soon gives rise to dilatation of the coronary vessels. This dilatation is almost proportional to the degree of anoxæmia, so that, within very considerable limits, it is found that the consumption of oxygen by the

heart is independent of the oxygen saturation of the blood. The effect of increasing deoxygenation of the blood on the coronary flow is shown in the accompanying diagram (Fig. 404).

This effect is probably to be explained as due to a direct effect of oxygen lack on the plain muscle of the coronary vessels; it is seen to occur at once when traces of cyanides are added to the blood, so as to suppress oxygen utilisation (Fig. 404). It has been ascribed to the action of metabolites produced in the heart muscle, but if this is so we have no idea of their nature.

Two of the metabolites, namely carbonic acid and lactic acid, which are known to be produced in the contraction of cardiac muscle, have a dilator influence on the coronary vessels, but this is slight compared with that of anoxæmia, and is probably due to the accompanying slight increase in hydrogen ion concentration.

(b) Woollard has shown that the coronary arteries are richly innervated from both the vagus and the sympathetic, and Anrep and Segall have found

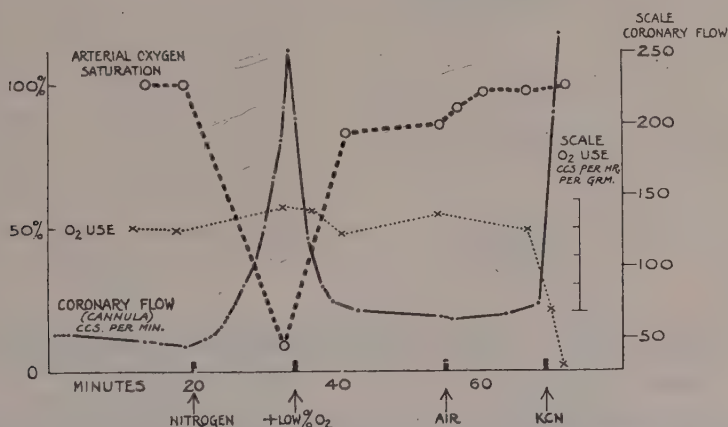


FIG. 404. Curves showing the Relation of the Coronary Blood Flow and of the Oxygen Consumption by the Heart to the Degree of Oxygen Saturation of the Blood passing through the Coronary Vessels. (HILTON and EICHHOLTZ.)

that the vagal fibres are constrictor to the coronary vessels and, like the cardio-inhibitory fibres, normally exhibit a tonic action. Section of the vagi, therefore, not only quickens the heart rate, but also relaxes the coronary vessels and allows an increased flow. Further, when the output of the intact heart is increased, there is, in addition to the reflex cardiac acceleration, also an independent reflex relaxation of the coronary vessels, whereby the circulation through the heart is increased: this is lost on section of the vagi, and is therefore not exhibited by the denervated heart-lung preparation, in which the effect of alteration of output has but little effect on the coronary flow. On stimulating the sympathetic nerve supply to the heart, there is an increased frequency and energy of contraction and the same effects are produced by the injection of a small amount of adrenaline into the blood stream. This increased beat is always associated with greatly increased coronary blood flow. It seems, therefore, most likely that the sympathetic nerves to the heart have a direct dilator effect upon the coronary arterioles.

The above factors may be all involved in the adaptation of the blood flow to the needs of the heart when the activity of this organ is increased, either by increased arterial resistance or by increased output, in both of which the oxygen usage of the heart is increased.

The influence of the various phases of the cardiac cycle upon the coronary flow has been the subject of many conflicting experiments and much debate in the past, which the work of Anrep and his collaborators has done much to illuminate. Anrep has studied the coronary inflow and outflow separately, and found that these do not run parallel. Fig. 405 shows the relation of these to other events of the cardiac cycle. The coronary outflow shows three waves, very similar to those seen in the intra-auricular pressure; the most

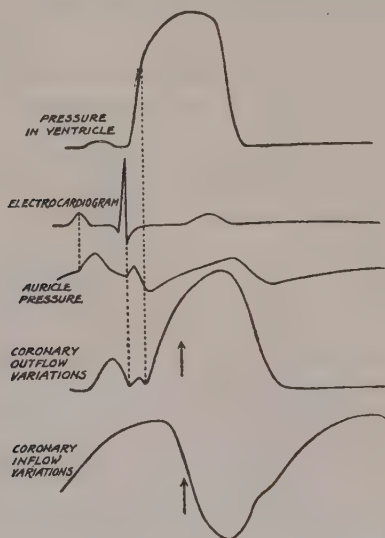


FIG. 405. Relation of Coronary Outflow and Inflow to other events of the Cardiac Cycle. The arrows point in the direction of increase of flow. (ANREP, *et al.*, "Heart," 1927.)

rapid flow is seen during ventricular systole, and is no doubt due to a massaging action of the ventricular contraction expelling blood from the coronary veins. The other waves of the outflow are probably due to the effects of auricular contraction. The variations of coronary inflow consist in a rapid entry of blood during diastole and early systole, which is suddenly checked as soon as ejection of blood from the left ventricle begins, and reaches its minimum at about the time that the coronary outflow is at its maximum, *i.e.* at the height of the systolic reduction of volume.

CHAPTER XXXIV

PHYSIOLOGY OF THE BLOOD VESSELS

BLOOD PRESSURE

SINCE the blood travels from the arteries to the veins, it is evident that the pressure which drives it onwards must get less and less as it passes along.

On cutting through an artery, blood escapes from the central end, *i.e.* that nearest the heart, with great force and in a series of jerks, each of which corresponds to a contraction of the ventricles. This manner of escape shows that in the arteries the blood is at a high pressure, and that the flow from the heart to the periphery is a pulsatory one. The same lesson may be learnt by connecting a long vertical tube with the central end of a divided artery. This experiment, which was first performed in 1732 by the Rev. Stephen Hales, may be described in his own words :

"In December I caused a mare to be tied down alive on her back. Having laid open the left crural Artery about three inches from her belly, I inserted into it a brass Pipe, whose bore was one sixth of an inch in diameter; and to that, by means of another brass Pipe which was fitly adapted to it, I fixed a glass Tube, of nearly the same diameter, which was nine feet in length: Then untying the Ligature on the Artery, the blood rose in the Tube eight feet three inches perpendicular above the level of the left Ventricle of the heart: But it did not attain to its full height at once; it rushed up about half way in an instant, and afterwards gradually at each Pulse twelve, eight, six, four, two, and sometimes one inch: When it was at its full height, it would rise and fall at and after each Pulse two, three, or four inches; and sometimes it would fall twelve or fourteen inches, and have there for a time the same Vibrations up and down at and after each Pulse, as it had when it was at its full height; to which it would rise again, after forty or fifty Pulses."

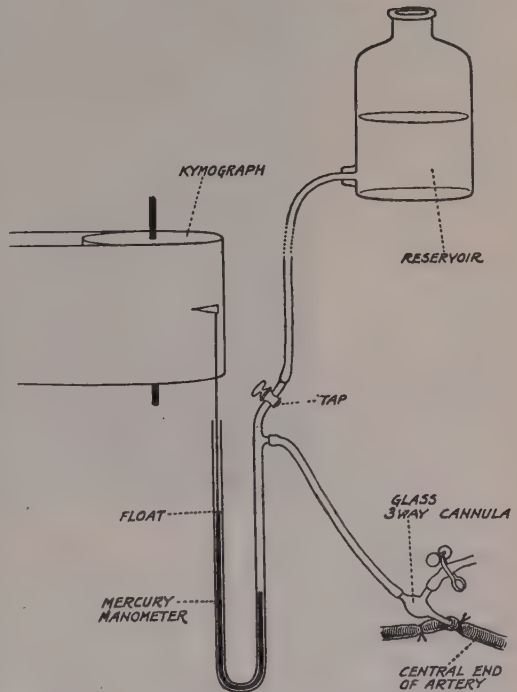


FIG. 406. Arrangement of an Apparatus for taking Blood Pressure Tracing.

The method adopted by Hales offers the very considerable drawbacks that the manipulation of such long tubes is awkward, and the blood which escapes into the tubes very soon clots. It is therefore customary to use a special manometer.

The *mercurial manometer*, which is much used for measuring and recording arterial pressure, consists of a U-tube with two vertical limbs about a foot in height, which is half-filled with clean mercury. On the surface of the mercury of one limb is a float of vulcanite from which a stiff fine rod of straw, glass, or aluminium rises, bearing on its upper end the writing-point. This point is adjusted so as to write on the travelling paper surface. Since the mercury is displaced equally, up in one limb and down in the other, it is obvious that any displacement as recorded must be multiplied by two to obtain the actual pressure in terms of a mercury column. The other limb of the manometer is connected by a side-branch and a flexible inextensible tube with a cannula, which is tied into the central end of an artery, a clip being previously placed on the artery so as to prevent the escape of blood. This limb is also connected, through a tap, with a reservoir bottle placed several feet above it, and filled with sodium citrate (1 per cent.) or with a half-saturated solution of sodium sulphate. First, this tap is opened and the manometer, connecting-tube and cannula filled with this solution. The tap is then closed so that the manometer remains in connection only with the cannula, the mercury in that limb being now, say, about 150 mm. above that in the other. The clip is then taken off the artery. The pressure in the cannula being greater than that in the artery, a small amount of the fluid used to fill the tubes runs into the circulation. The mercury in the manometer drops to a height, usually of 100 to 120 mm. Hg., and stays about that level, rising and falling slightly with each heart beat (Fig. 406). The blood which enters the cannula at each heart beat does not clot for a considerable time, owing to its admixture with the saline fluid used for filling the cannula and connecting tubes.

For more accurate records of the pulsations, the mercury manometer can be replaced by a membrane manometer of the Hürthle or Wiggers pattern, such as is employed for endocardiac pressure records.

If a vein be ligatured, it swells up on the distal side of the ligature.

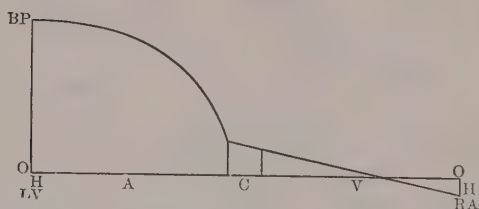


FIG. 407. Scheme of Blood Pressure in—A, the Arteries; C, Capillaries; V, Veins; and H, Heart oo. Line of no pressure.
LV. Left ventricle.
RA. Right auricle.
BP. Height of blood pressure.

If the vein be cut across, blood escapes chiefly from the peripheral end, and instead of spurting out with each heart beat, it flows steadily but with very little force, so that light pressure by a bandage is sufficient to restrain the hæmorrhage. If a mercurial manometer be connected with the vein, the pressure in its interior is found to amount to only a few millimetres Hg. It is therefore customary to

use manometers filled with an aqueous solution, *e.g.* sodium citrate, for venous pressure experiments.

By taking the pressure at different parts of the circulation, we obtain a distribution which is represented roughly in the accompanying diagram (Fig. 407). The blood pressure, which is about 100 to 120 mm. Hg. in the large arteries near the heart, falls only slowly in these arteries, so that in the radial artery it is not very much below that in the aorta. Between the medium-sized arteries and capillaries there is a very extensive fall of pressure as the blood passes through the arterioles, so that in the capillaries the pressure on an average may be taken as 10 to 20 mm. Hg.; from the capillaries to the veins the blood pressure falls steadily until in the big veins near the heart it may be negative.

THE ARTERIAL BLOOD PRESSURE. The arterial blood pressure as recorded by a mercurial manometer exhibits a series of pulsations corresponding to each heart beat (Fig. 408). These pulsations are due to the fact that the artery becomes fuller each time the ventricle forces more blood into it during its systole. Between the beats of the heart, *i.e.* during

diastole, the aortic valves are closed, and blood escapes from the arteries into the capillaries and veins, so that the blood pressure falls. The mercurial manometer, however, owing to the inertia of the heavy column of mercury, does not register these rapid changes of pressure in the artery with any accuracy. With a very wide-tubed manometer, in fact, the oscillations may be almost imperceptible. But it gives a true and valuable record of what is known as the 'mean arterial pressure.'

In order to determine the true course of the pressure changes in the arteries, it is necessary to diminish to the utmost possible extent the inertia of the moving parts of the recording instrument, as in Hürthle's

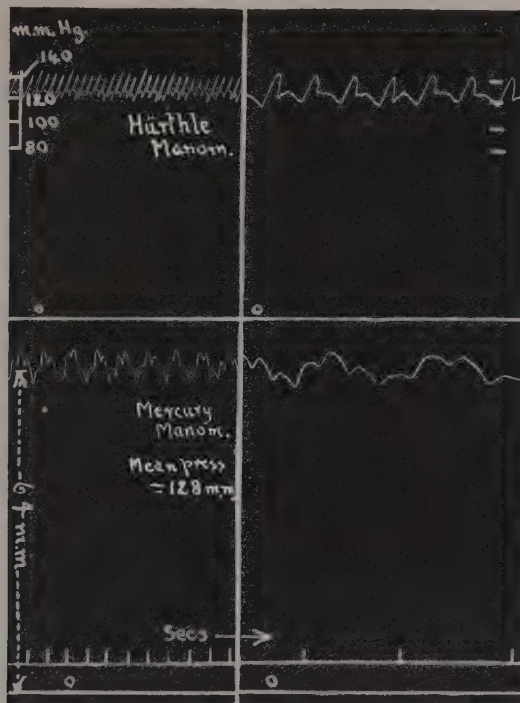


FIG. 408. Arterial Blood Pressure from carotids of Dog, recorded simultaneously with Hürthle Manometer (upper tracing) and Mercury Manometer (lower tracing), on slowly and rapidly moving surfaces. The form and extent of each pulse is much more correctly shown by the Hürthle Manometer, but the slower changes due to respiration are more evident with the Mercury Manometer. 0 = line of zero pressure. The left-hand half is on a slowly moving, and right hand on rapidly moving surface. (C. L. E.)

membrane manometer, or better still one of the forms of manometer in which the pressure changes are registered photographically. Examination of records obtained by these superior methods (Figs. 395 and 408) shows that the variation in the arterial pressure at each heart beat is much greater than would be anticipated from an inspection of the tracing given by the mercurial manometer. The highest pressure which occurs while blood is passing from the heart into the aorta is called the *systolic arterial pressure*; the pressure at the end of diastole, just before the heart begins to force a fresh quantity of blood into the aorta, is the *diastolic pressure*; and the range between these two extremes is known as the *pulse pressure*. In man the systolic pressure, as measured in the brachial artery, is under normal conditions about 110 mm., while the diastolic pressure is only 65 to 75 mm.,

so that the pulse pressure is about 45 mm. Hg. As we pass outwards towards the periphery the pulse pressure becomes less and less marked, until finally, in the capillaries and veins, there is no pulse wave perceptible.

THE DETERMINATION OF THE BLOOD PRESSURE IN MAN

ARTERIAL PRESSURE.—It is important for clinical purposes to be able to determine, if only approximately, the blood pressure in the different parts of the vascular system in man, and various methods have been devised for this purpose. The determination of the systolic blood pressure in the arteries is easily carried out by the use of Riva Rocci's sphygmomanometer. This apparatus (Fig. 409) consists of a leather or canvas band about 10 cm. wide, which can be buckled closely round the upper arm. Inside this band is a rubber bag of the same shape, which communicates by a rubber

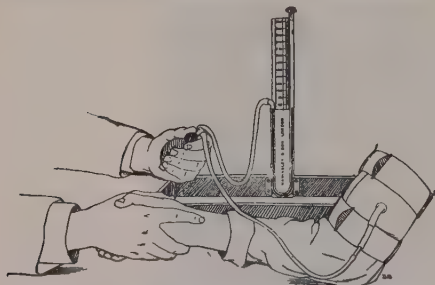


FIG. 409. Riva Rocci's Sphygmomanometer.
(O. J. Martin's pattern. HAWKESLEY.)

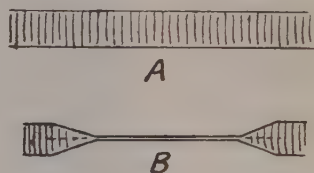


FIG. 410.

tube with a mercurial manometer and by a three-way tap either with an air pump, or with the external air. The band is buckled round the arm and the fingers of the observer are placed on the radial pulse. The bag is then distended with air so that it exercises a pressure on the arm, the pressure being indicated on the mercurial manometer. Air is forced in until the radial pulse disappears. By means of the three-way tap the air is then let slowly out of the bag until the radial pulse is just perceptible. The height of the mercurial manometer at this moment is equal to the systolic pressure in the main arterial trunk from which the brachial artery takes origin. The principle of this method will be made clear by reference to the diagram (Fig. 410). If we imagine A as a segment of the brachial artery passing through the tissues which are surrounded by the rubber bag, we see that so long as the pressure in the interior of the artery is greater than that exerted by the tissues on the exterior, the artery will be patent and the pulse can pass through. If, however, the pressure in the tissues becomes greater than the maximum pressure inside the artery at any time of the heart beat, the segment of artery will collapse (as in B), thus stopping the transmission of blood and of the pulse wave. If we exclude the elasticity of the tissues themselves,

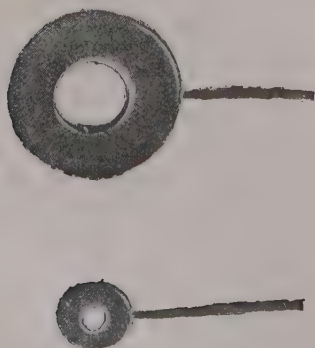


FIG. 411.

we may take the pressure in the bag as representing the pressure in the tissue fluids surrounding the artery, so that the pulse-obliterating pressure in the bag will correspond to the maximum or systolic pressure in the artery.

By a slight modification of the apparatus it is possible to determine also the diastolic pressure. For this purpose the rubber bag is connected also with a manometer of small inertia, giving a true representation of the actual changes of pressure. It is evident that when the pressure in the bag, and in the tissues surrounding the artery, just exceeds the diastolic pressure, the artery will be completely collapsed in diastole, and will then dilate almost to the utmost with the systolic rise of pressure. If we are taking a record of the pressure changes in the bag in this way, the pulse waves as recorded by the manometer will slowly increase in size as the pressure in the bag is gradually raised from zero. At

one point the waves rapidly increase and reach a maximum, and the pressure in the bag at this point is taken as the diastolic pressure. As the pressure is still further

raised, the excursions of the manometer diminish again, first slowly and then rapidly, and the point of rapid diminution corresponds to the systolic pressure. Above this point the manometer still shows small oscillations, due to the impact of the unoccluded stump of the artery on the upper border of the india-rubber bag.

THE AUSCULTATORY METHOD. The most convenient method of finding the approximate value of the systolic and diastolic pressures in the artery is to apply the bell of a binaural stethoscope over the brachial artery a little distance below the cuff of the Riva Rocci apparatus. When the cuff is first rapidly inflated to a point beyond the extinction of the pulse, and then gradually deflated, a series of sounds are heard, divided by Wiggers into five periods :

- (1) As the pressure falls there is a sudden appearance of a clear sound, as the first flow of blood occurs through the compressed artery. This corresponds to the *systolic pressure*.
- (2) The sound becomes more continuous, like a murmur.
- (3) The sound becomes progressively louder.
- (4) The sounds suddenly become muffled.
- (5) The sounds disappear.

According to most observers the phase (4) corresponds to the diastolic pressure.

VENOUS PRESSURE. To determine the venous pressure in man we may use some modification of von Recklinghausen's method. A circular, disc-shaped, incomplete rubber bag (Fig. 411) is made by cementing together at the circumference two rubber discs, each of which has a hole in the centre. This is placed over a peripheral vein and a glass plate laid on the top (Fig. 412). A tube leads from the interior of the

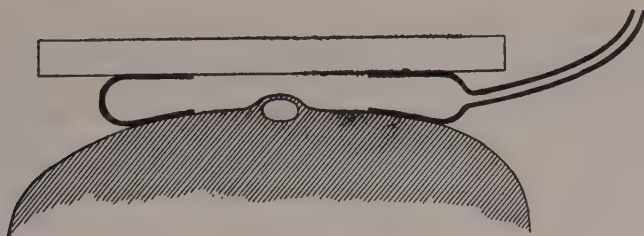


FIG. 412.

annular rubber bag to a water manometer and to an air pump for the injection of air. On blowing air into the bag the pressure in its interior rapidly increases. If the skin and glass plate have been previously smeared with glycerin, the air does not escape but distends the bag, pressing it against the skin on the one hand and the glass plate on the other. Through the hole in the rubber bag it is easy to see the pressure at which the vein collapses—that is to say, the point at which the pressure in the bag is equal to the pressure within the vein.

By a similar method, using a smaller bag, we may determine the pressure which is just sufficient to obliterate the capillaries in any given area of the skin, so causing a blanching of the skin lying under the bag.

The following Table may serve to give an idea of the average height of the *mean* blood pressure (not systolic) at different parts of the vascular system in a young adult man, in the horizontal position. The pressures are all subject to considerable variations according to the activity of the individual and of the various parts and organs of the body :

Large arteries (<i>e.g.</i> carotid)		90 mm. mercury (65–110).
Medium arteries (<i>e.g.</i> radial)		85 mm. „
Capillaries	 about	10 to 30 mm. mercury.
Small veins of arm		9 mm. mercury.
Portal vein		10 mm. „
Inferior vena cava		3 mm. „
Large veins of neck	 from	0 to –8 mm. mercury.

The cause of the gradients in the circulation in different parts of the vascular system will be rendered clearer by a study of a flow of fluid through a tube of uniform bore

(Fig. 413). If the tube AG be connected with the reservoir R , fluid will flow out from G under the influence of hydrostatic pressure. The pressure on the fluid at each part of the tube can be measured by attaching at a series of points—*e.g.* at B , C , D , E , F —vertical tubes in which the fluid will rise to a height corresponding to the lateral pressure existing at these several points. If AG is of uniform bore, it will be found that the heights of the fluid in the tubes show a continuous descent, so that the line joining the tops of the fluid

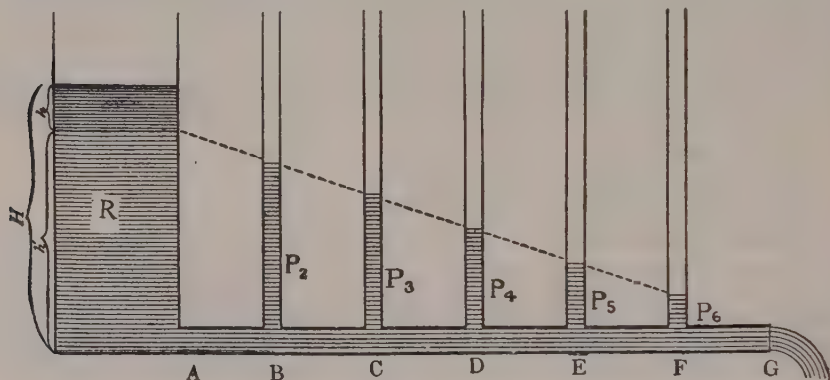


FIG. 413.

in the various tubes is a straight one. The movement of the fluid from B to C can be regarded as due to the difference of the pressure between B and C , *i.e.* $P_2 - P_3$. It will be noticed in the diagram that the straight line joining the tops of the fluid does not strike the surface of the fluid in R , but falls a little below it. Of the total pressure H in R , the large portion h' is employed in overcoming the resistance of the tube AG , while a small portion h represents the force necessary to give to the fluid as it leaves the reservoir at A a certain velocity. If the flow of fluid be diminished by partially clamping the end at G , the rate of fall of the pressures will be diminished. The same effect will be

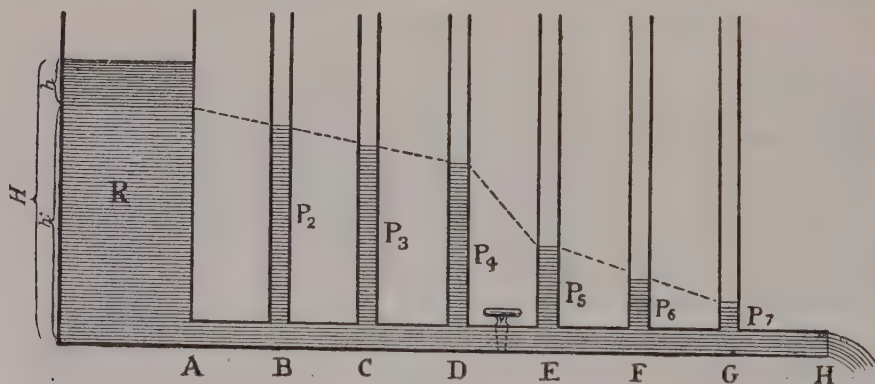


FIG. 414.

produced either by raising the level of G or by lowering the level of the reservoir and so the pressure at A .

The difference of pressure between any two points, *e.g.* between D and E , may be regarded as that pressure which is necessary to maintain a certain velocity of the fluid against the resistance offered by the friction of the fluid in contact with the walls of the tube. This friction, and therefore the resistance to the flow, can be altered by diminishing the diameter of the tube, when a larger difference of pressure will be necessary in order to maintain the same velocity of flow. This can be shown by introducing a resistance between D and E by partially clamping the tube at this point (Fig. 414). The continuity of the fall of pressures in the vertical tube is at once abolished. Between A and D there is a continuous fall, which is succeeded by a steep fall between D and E , and this again by a gradual fall between E and G . In any system of tubes,

therefore, through which fluid is flowing, the fall of pressure between any two points will be proportional to the product of the velocity and the resistance to the flow between these two points. The velocity on the other hand will vary directly as the difference of pressures, and inversely as the resistance between the two points. These relations may be expressed by the formula :

$$V \propto \frac{P}{R}$$

In the living vascular system, the largest difference of pressure exists between the arteries on the one side and the small veins on the other, a great fall occurring between the arteries and the capillaries themselves. This distribution of pressure points to the chief gradient in the vascular system as being situated in the arterioles. The resistance presented by these vessels is due to their small calibre, since they are maintained in a state of tonic contraction. The total bed of the stream in the region of the arterioles, while greater than that of the arteries, is considerably less than that of the rich meshwork of capillaries, while the difference between the diameters of arterioles and dilated capillaries is not very large. On this account the velocity of the blood in the arterioles is very much greater than that obtaining in the capillaries, and since friction, and therefore the resistance, varies as the square of the velocity, the resistance to the flow of blood through the arterioles must be greater than that often presented by the capillaries. When the capillaries constrict, however, they also add largely to the peripheral resistance. The large part taken by the arterioles in determining the difference of pressure between the arteries and veins is shown by the fact that this difference can be diminished to one-half by any means which causes a general dilatation of the arterioles, as for example destruction of the vaso-motor centre.

The mean arterial pressure, *i.e.* the average pressure within the arteries at any given time, is thus dependent on :

(1) The resistance to the outflow of blood from the arterial system, *i.e.* on the state of constriction of the arterioles and, to a smaller extent, of the capillaries.

(2) The output of the heart per unit of time. Another factor of great importance is the total capacity of the vascular system in reference to the total volume of circulating blood. The manner in which this works may now be discussed.

INFLUENCE OF THE CAPACITY OF THE VASCULAR SYSTEM

So far, we have considered only the influence of changes of pressure and resistance in a simple tube with a head of pressure at one end and a free outflow at the other. In the body, however, the vascular system is a closed circuit of branched elastic tubes presenting varying resistances to the flow of blood, and of varying diameters and distensibility at different parts of their course. In this closed system is inserted a pump, the heart, which drives the blood through the system. Since all the blood vessels are elastic and distensible, the capacity of the system must vary with the internal pressure to which the vessels are subjected. Moreover, the position of the different parts of the body must have an influence on the capacity of the system, since the dependent vessels will be distended, not only by the average pressure of the fluid throughout the system, but also by the hydrostatic pressure due to the weight of the column of fluid pressing on them. The elasticity of the tubes is also a varying factor, and can be considerably altered by the contraction of the muscular coats of the vessels, or by pressure on the vessels exerted by the surrounding muscular and elastic structures.

It will simplify the discussion of the main factors of the circulation in a closed system if, for the present, we neglect the variable factors and see what would take place in such a system of elastic tubes all situated on one horizontal plane. Such a system is represented in the diagram (Fig. 415), and a working model of it in Fig. 416.

The heart *H* is interpolated at one part of the circuit, while the free flow of the fluid from *B* to *D* is impeded by the presence of a peripheral resistance at *C*. Such a system would have a definite capacity at zero internal pressure, but a very much greater amount of fluid might be forced into it under a positive pressure. We will assume that the pressure throughout the system when at rest is 10 mm. Hg., *i.e.* the elastic tubes are all slightly distended. If the heart *H* now begins to contract, it will pump fluid from *E* into *A*. The pressure in *E* will fall to 0 mm., while that in *A* will rise to a corresponding extent, the resistance at *C* preventing the free escape of fluid from *B* to *D*, and so causing the heart to pile up the fluid which it has taken from *E* into *A*.

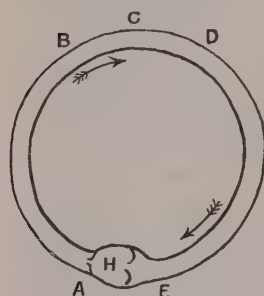


FIG. 415.

If the texture of the tubes were uniform throughout the system, the rise of pressure in *A* would approximate very nearly to the fall of pressure in *E*. In the vascular system the veins are, however, much more easily distended by low pressures than the arteries (Figs. 345 and 346). The vein is collapsed when there is no distending force in its interior, so that at zero pressure its capacity is nothing. The slightest rise of pressure causes a considerable increase in its capacity, and the capacity rises rapidly with increasing

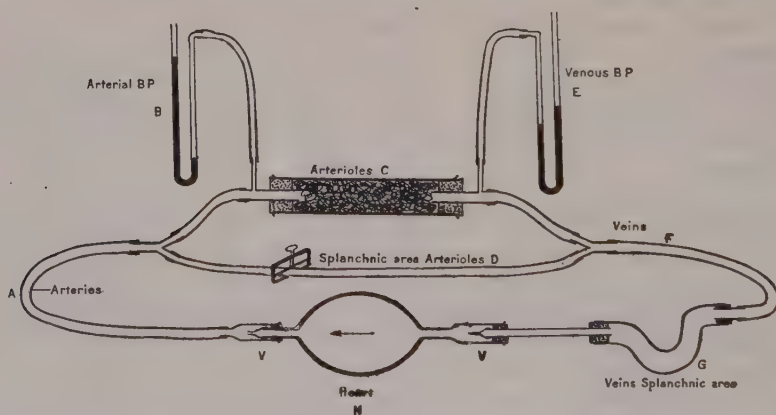


FIG. 416. Artificial Schema to Demonstrate the Main Features of the Circulation.

The heart is an enema syringe with valves at *v* and *v*. The artery is a thick-walled rubber tube. On the venous side is placed a length of wide thin-walled tubing, to represent the large thin-walled distensible veins. The arterioles and capillaries (peripheral resistance) are represented by wide glass tubes packed with sponges. By opening the clamp on the tube *D* ('splanchnic area arterioles') the peripheral resistance can be removed, and a free passage of fluid allowed from arterial to venous side.

pressure up to about 20 mm. Hg. Whereas the artery needs a pressure of about 100 mm. Hg. to distend it, and continues to stretch, but more

slowly, at higher pressures, the vein is distended almost to its maximum at about 10 mm. Hg. If, therefore, the tubes at E are made of thin-walled rubber tubing, they will be considerably distended under a pressure of 10 mm. Hg., which has practically no influence on the thicker-walled arterial tube A.

A small amount of fluid taken from E would thus cause very little fall of pressure on this side. A considerable force will be necessary to send this fluid into the more resistant arterial tube, so that on pumping enough fluid from E to A to lower the pressure in E, say 5 mm., the pressure in A has to be raised to, say, 100 mm. Hg. in order to distend the arteries to such an extent that they will accommodate the fluid.

In such a system, when the heart contracts, it takes fluid from the veins to the arteries, and piles up the pressure on the arterial side until it is sufficient to cause fluid to flow through the peripheral resistance into the veins at the same rate as it is taken by the heart from the veins. This rise of pressure in the arteries may be many times greater than the fall of pressure in the veins. If more fluid is injected into the system, the whole system will be more distended and the *mean systemic pressure* will rise. Then the heart will raise the pressure on the arterial side and lower that on the venous side as before, but according to the rate of output by the heart, the arterial pressure may be less than, equal to, or greater than the pressure attained before the introduction of fluid. Supposing it to be the same as before, the increased amount of fluid must be accommodated somewhere, so that the venous pressure must be greater. In the same way, the withdrawal of a certain amount of fluid may lower the mean systemic pressure, and it would still be possible for the pump to maintain an arterial pressure equal to that produced when the mean systemic pressure was 10 mm. Hg., but to obtain this effect the rate of its output would have to be increased, and the veins must be more empty than they were previously. The maintenance of a constant arterial pressure with varying amount of fluid in the system can therefore be accomplished either by alterations in the output of the heart or by alterations in the peripheral resistance, and therefore in the ease with which the blood is allowed to escape from the arterial to the venous side.

Alterations of the capacity of the system will have the inverse effect to alterations of its contents. Thus diminution in the volume of veins, such as might be caused in the living body by pressure on the veins from without, and which may be imitated in our model, will drive the fluid into other parts of the system and therefore raise the mean systemic pressure. This rise of pressure may be confined to the arteries by increased action of the heart, or it may be confined to the veins by diminished action of the heart or decreased constriction of the arterioles forming the peripheral resistance.

Similar change in capacity may be brought about by alterations in the hydrostatic pressure in the vessels. If, in the model illustrated (Fig. 416), we allow the thin-walled vein to hang over the edge of the table, the pressure of the column of fluid within it causes it to dilate and therefore to accommodate more fluid, and this increased capacity might be so great that the pressure in the section of the vein near the heart might sink to nothing, and the heart receive no blood when it started to contract. The whole arterial system might in this way be allowed to drain under the influence of gravity into the distensible dependent segment of the venous tube.

All the conditions in our artificial schema have their exact analogue in the living body. The determination of the mean systemic pressure in

the living body is difficult to carry out with accuracy, but the fact that after stoppage of the heart, the pressure is positive at all parts of the vascular system in the animal with open thorax, shows that there is actually a mean systemic pressure, *i.e.* under normal circumstances, when the animal is in a horizontal position, all parts of the system are slightly distended. Direct measurement shows that this mean systemic pressure is about 10 mm. Hg. The smallness of this figure shows moreover that, under the influence of gravity alone, the pressure will be easily reduced to nothing at all in the upper parts of the body. In a man in the vertical position, in the absence of the nervous reactive mechanism which we shall consider later on, the whole of the blood would accumulate in the abdomen and lower parts of the body, and the circulation would come to a standstill.

On the other hand, widespread or universal dilatation of the capillaries, as may occur under the influence of poisons such as histamine, or in the state of surgical shock, may so increase the total capacity of the vascular system that the blood remains in the capillaries and an ever decreasing amount of blood is available to press on into the heart. The heart thus has a diminished output, and is unable to maintain the normal arterial pressure in the arterial system. Thus the pressure may be altered in any part of the vascular system in any of the following ways :

(1) Alteration of capacity of the total system, either by contraction of the walls of the vessels or by pressure on them from without.

(2) Alteration of the total volume of the circulating fluid.

Either of these two factors would affect, in the first place, the mean systemic pressure. The distribution of pressure, *i.e.* the relative pressure in the arteries and veins, will be determined by

(3) Alteration in the output of the heart. This may be augmented by greater amplitude of ventricular contraction increasing the output per beat, or by greater frequency of beat. Generally both means are employed.

(4) Alteration in the peripheral resistance and therefore in the ease with which the blood can escape from arterial to venous side.

In any change, either in arterial or venous pressure, at least two of these factors are involved. Every constriction of arterioles causes, not only an increase in the peripheral resistance, but also a diminished capacity of the whole system, so that the arterial pressure is raised at the same time as the mean systemic pressure. Nearly always such a change will involve as its immediate consequence some corresponding alteration in the heart beat, so that at least three factors will co-operate in the production of the rise or fall of blood pressure.

THE DEPENDENCE OF ARTERIAL PRESSURE ON OUTPUT OF HEART. Arterial pressure is a resultant of the two effects :

(a) The rate at which blood enters the arterial system from the heart ;

(b) The rate at which blood leaves the arterial system through the peripheral resistance.

It is evident that the pressure will be altered by varying either of the two factors—peripheral resistance or output of the heart. The cardiac output will depend on the stroke volume of the heart and on the pulse rate. The filling of the heart at the beginning of each beat is in its turn dependent on the pressure in the great veins. If the heart is beating with optimum rate and force, it will keep the venous system, at any rate that part nearest the

heart, practically empty, and it is not possible for it to obtain more blood to put into the arterial side, however frequently it may beat. Increased frequency of heart beat does not, therefore, necessarily increase the total output of the heart into the arterial system. There will be an optimum frequency of the heart beat which will depend on the state of filling of the great veins. The fuller these are, the more the total output can be augmented by an increase of the heart rate. On the other hand, in a normal animal with the heart beating at its optimum rate and with effective contraction of its muscular walls, slowing the heart rate will diminish the total output and therefore the arterial pressure.

THE CONVERSION OF AN INTERMITTENT INTO A CONSTANT FLOW

By the time it has arrived in the veins, the flow of blood has been converted from a pulsatory into a continuous flow. This change, which is a purely mechanical one, is connected with the elastic nature of the arterial walls and will be more easily understood by a simple illustration. The heart forces a certain amount of blood (in man about 60 c.c.) into the circulation at each stroke. If a pump be connected with a rigid tube, every time that a certain amount is forced into the beginning of the tube an exactly equal quantity will be forced out at the other end. Increasing the peripheral resistance by partial closure of the end of the tube will not affect the intermittent character of the flow, but will merely serve to increase the force necessary to expel the same volume of fluid as before. If, instead of a rigid tube, we employ an elastic tube, and the end be left open so that no resistance is offered to the outflow, the outflow will, as with a rigid tube, correspond exactly to the inflow and will be just as intermittent. But now, if the end of the elastic tube be narrowed so as to increase the resistance to the outflow, there will be a marked difference from the results obtained when the rigid tube was partially obstructed. Each stroke of the pump forces the same amount of fluid into the tube as before, but owing to the peripheral resistance this does not now all escape at once; instead, part of the force of the pump is spent in raising pressure and distending the walls of the tube and part of the fluid that was forced in remains in the tube. The distended elastic tube tends to empty itself and force out the fluid which over-distends it before the next stroke of the pump occurs. So now the outflow may be divided into two parts, one part which is forced out by the immediate effect of the stroke of the pump, and another part which is forced out by the elastic recoil of the tube between the strokes. If the strokes be rapidly repeated before the tube has time to empty itself thoroughly, it will get more and more distended. Greater distension means stronger elastic reaction, and therefore a larger outflow of the fluid between the beats. This distension goes on increasing till the fluid forced out between the strokes by the elastic reaction of the wall of the tube is exactly equal to that entering at each stroke, and the flow thus becomes continuous.

The same thing occurs in the living body. A man's heart at each beat forces about 60 c.c. of blood into the already distended aorta. The first effect of this is to distend the aorta still further. The elastic reaction of the walls drives on another portion of blood, which distends the next segment of the arterial wall, and so the wave of distension is transmitted with gradually decreasing force along the arteries. This wave of distension is what we feel

on the radial artery or any exposed artery as the pulse. After each heart beat the arteries tend to return to their original size, and drive the blood onwards. By the time the blood has reached the veins, all trace of the heart beat has disappeared, and the pressure has fallen to a few millimetres of mercury.

THE VELOCITY OF THE BLOOD AT DIFFERENT PARTS OF THE VASCULAR SYSTEM

When fluid is flowing through a tube of uniform diameter, the amount passing between any two points varies directly as the difference of pressure between these two points, and inversely as the resistance to be overcome. If

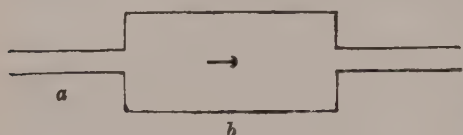


FIG. 417.

the tube is of unequal bore, as represented in Fig. 417, since the amount of fluid passing *a* during a given interval of time must be equal to the amount passing *b*—where the bed of the stream is wider, the velocity of the flow must be smaller at *b* than at *a*.

The same dependence of velocity on the total bed must apply in any system of tubes. Thus in a closed circuit (Fig. 415) with a steady flow from the arterial to the venous side, the amount of fluid passing *a* during a minute must be exactly equal to the amount passing through the peripheral resistance *c*.

The total area at *c* is, under average conditions, probably one thousand times that of the aorta at *a*, and we should expect therefore a proportionate slowing of the blood stream. As a matter of fact, while the mean velocity of the blood in the aorta of a large animal may be taken as about half a metre per second (varying at different parts of the cardiac cycle from 0.1 to 1.0 metre per second), the velocity of the blood in the capillaries is about half a millimetre per second. Moreover, since the total cross section of the big veins near the heart under a normal distending pressure is about twice that of the first part of the aorta, the velocity of the blood in the great veins is only about half of that found in the aorta. In such a closed circuit, increased output of the heart will increase the average velocity round the system, and the same effect may be produced by diminution of the peripheral resistance.

In the living body a great dilatation of the arterioles, causing a fall of the peripheral resistance, also increases the total capacity of the system. The arterial relaxation, therefore, not only gives rise to an easier outflow from arteries to veins, but also causes a diminished filling of the veins, and therefore of the heart during diastole. The heart output is therefore also lessened, so that a final result of a dilatation of the arterioles may be a diminished, instead of an increased, velocity throughout the system.

The foregoing discussion of the factors which determine the average velocity through a given cross section of the whole vascular system, must not be applied directly to the changes in the velocity following on *local* alterations in the resistance presented by some particular vascular area. In this case the local changes are insufficient to affect the general arterial blood pressure, and the result of diminution of peripheral resistance is to furnish a short cut for a small portion of the total output of the heart from

the arterial to the venous side. Thus dilatation of the vessels of the sub-maxillary gland, while not altering the general blood pressure, causes the blood flow through the gland to be increased six to eight times; and the peripheral resistance in the gland may be so far diminished that the blood passes into the veins without losing the pulsatile force imparted to it by each heart beat. The pressures, therefore, in arterioles, capillaries and veins are all increased by this local vaso-dilatation. On the other hand, constriction of the arterioles of any given part will diminish the velocity of the blood through this part and also the pressure in its capillaries.

The larger the area affected by the change in the peripheral resistance, the more difficult it is to predict *a priori* what will be the result on the velocity of the blood and on the circulation as a whole, or in the parts specially affected. Thus, section of one splanchnic nerve in the dog causes an increased flow of urine from the kidney on the same side, the paralysis of the vessels in this organ causing an increased flow of blood through it and an increased pressure in its capillaries. Section of the corresponding nerve of the rabbit may cause a diminution in the amount of urine secreted, because the total area supplied by the splanchnic nerve is much

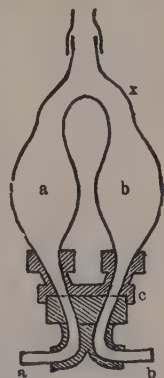


FIG. 418. Diagram of Ludwig's 'Stromuhr.'

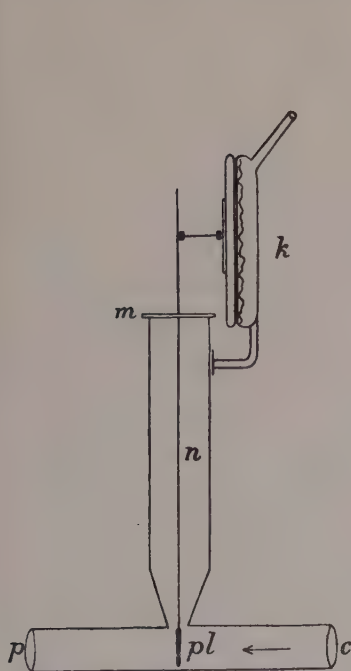


FIG. 419. Diagram showing the Construction of Chauveau's Hemadromograph.

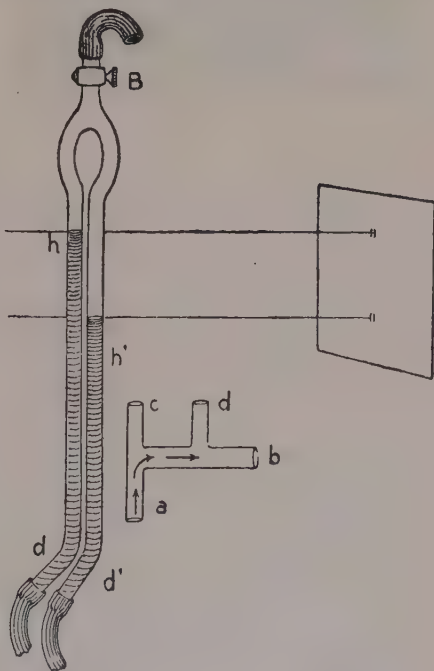


FIG. 420. Diagram to show Principle of Construction of Cybulski's Photohematometer.

greater relatively in the rabbit than in the dog, and section of this nerve may cause such a fall of arterial pressure that it is not sufficient to drive through the relaxed vessels as much blood as was previously driven through the normally contracted arterioles.

METHODS OF MEASURING THE VELOCITY OF THE BLOOD

If we can measure the average volume of blood passing along an artery per minute, we can calculate the mean speed of its movement by dividing this by the cross-sectional area of the artery. The mean flow can be measured by Ludwig's *Stromuhr* (Fig. 418). This instrument consists of two bulbs of equal size, *a* and *b*, communicating with one another above; their lower ends are clamped in the disc *c*, which is pierced by two openings serving to connect the lower orifices of the bulbs with the tubes cemented into the lower disc *ab*. The animal is first given an intravenous dose of heparin to render the blood incoagulable.

The artery being clamped at its central end and divided, *a* is inserted into its central end, and *b* into its peripheral cut end. The tube *a* is filled with oil and *b* with salt solution or defibrinated blood. On unclamping the artery, blood flows into *a* and drives the contained oil over into *b*, the contents of *b* being meanwhile forced into the peripheral end of the artery. When blood has completely filled the bulb *a*, the two bulbs are reversed, and the blood now entering the artery displaces the oil in *b*, and forces the

blood which had entered *a* on into the peripheral end of the artery. Knowing the capacity of the bulbs and the number of times it has been necessary to turn them in the course, say, of one minute, we know also the amount of blood which has passed through the artery under experiment, and by calculation its mean velocity.

This, however, does not give any information of the rapid changes occurring in the velocity of the blood during a single pulse wave. For this purpose we must have recourse to some instrument such as Chauveau's hæmadromograph or Cybulski's photohæmatachometer. The hæmadromograph (Fig. 419) consists of a pendulum which is hung in a tube, through which the blood is allowed to flow, placed

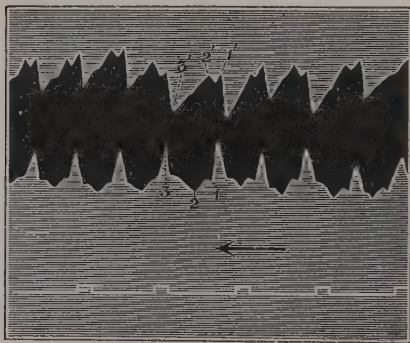


FIG. 421. Record of Blood Velocity in the Carotid Artery of the Rabbit. (CYBULSKI.)

in the course of the artery. The deviation of this pendulum from the vertical will be in proportion to the velocity of the current, and if its upper end be connected, as in the diagram, with a tambour, the variations in velocity can be recorded on a blackened surface by means of a lever. The *photohæmatachometer* is based on an interesting application of Pitot's tubes. If a current of blood be directed along the tube *ab* possessing two vertical side tubes *c* and *d* (Fig. 420), the pressure at *c* will be greater than that at *d*, since at *c* the momentum of the moving mass of blood is added to the lateral pressure of the fluid. A tube of this shape is connected with an artery such as the carotid, and the tubes *h* and *h'* are attached at the points *c* and *d*. These two tubes are united at their upper extremities. In this case, so long as the blood flows from *a* to *b*, the fluid in *h* will rise higher than in *h'*, and the difference in height of the fluid in the two tubes will be proportional to the velocity of the blood. A graphic record of this difference of pressure is obtained by allowing a narrow beam of light to throw an image of the menisci of the two columns of fluid through a slit on to a moving photographic plate. Such a record is given in Fig. 421. The width of the black space at any point is proportional to the velocity of the blood at the moment at which this part of the record was being taken. Of course this instrument has to be calibrated if we wish to determine the velocity of the blood in absolute measure. In Fig. 421 the velocity at the points 1 and 1', corresponding to the cardiac systole, was about 250 mm. per second. At 2 and 2', corresponding to the diastolic elevation, the velocity was about the same. At 3 and 3', towards the end of diastole, the velocity sank to 127 mm.

The velocity of the blood in the capillaries can be measured by direct observation of the capillaries under the microscope, and noting the time it takes for a blood corpuscle to move from one edge of the field to the other.

During systole the velocity of the blood in any part of the arterial system must be greater than during diastole; thus in the carotid of the horse the following figures were found:

					Velocity per second.
During systole	.	.	.	.	520 mm.
During diastole	.	.	.	.	150 mm.

The following figures of the average velocity have been obtained from experiments on dogs (Tigerstedt):

Body weight	Artery	Volume per second	Linear velocity per second	Diameter of artery	B.P.	Remarks
kg. —	Crural.	cc. 0.63	mm. 128	mm. 2.5	min. Hg. 77	Nerves un-injured.
14.6	Crural.	1.69	275	2.8	88	Nerves cut
14.1	Carotid.	1.95	241	3.3	93	Nerves un-injured.

THE ARTERIAL PULSE

The systolic rise of pressure at each heart beat causes an expansion, which can be felt by the finger placed on any exposed artery, such as the radial, and is spoken of as the pulse. As we have seen, the amplitude of the pulse decreases as we go farther away from the heart.

If the arterial system were perfectly rigid, the increased pressure at each ventricular systole would occur practically simultaneously at every point. The arteries are, however, elastic and distensible, so that the first effect of the

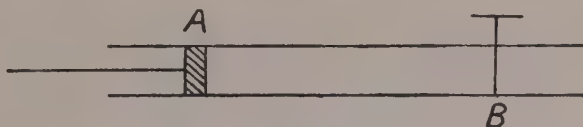


FIG. 422.

flow of blood into the aorta is to distend the section of the aorta nearest to the heart. The shock due to this suddenly increased tension is transmitted from segment to segment of the arteries in the form of a wave, at the velocity of about seven metres per second.

It is important not to confuse the velocity of the pulse wave with that of the blood flow; the latter is never greater than 0.5 metre per second, and is very much less than this in the smaller arteries. Perhaps the difference between the two quantities may be made clearer by illustration. If the hindmost of a row of billiard balls be struck sharply with a cue, the foremost ball flies off and the others stop still; in this case, the energy imparted to the first ball by the stroke has been transmitted from ball to ball, just as the effect of the ventricular contraction is transmitted from section to section of the arterial blood stream. If the balls are struck so that the cue continues pressing on the hindmost after the stroke is delivered, the front ball flies off, while the others move slowly along in the direction of the stroke. In the arteries, this continuous pressure is furnished by the elastic reaction of the arterial wall, and we see how the impact of the blood may travel quickly as a wave of increased pressure, while the blood itself is moving slowly along, impelled by the reaction of the arterial wall.

If we imagine a rigid tube AB (Fig. 422) provided with a piston at the end A, and filled with an incompressible fluid, an inward movement of the piston at A will cause a simultaneous outflow of fluid at the end B. If the end B is closed, the piston at A cannot be moved at all. Pressure applied to the piston will raise the pressure simultaneously at all points in the tube AB. The increased pressure applied at A is therefore transmitted

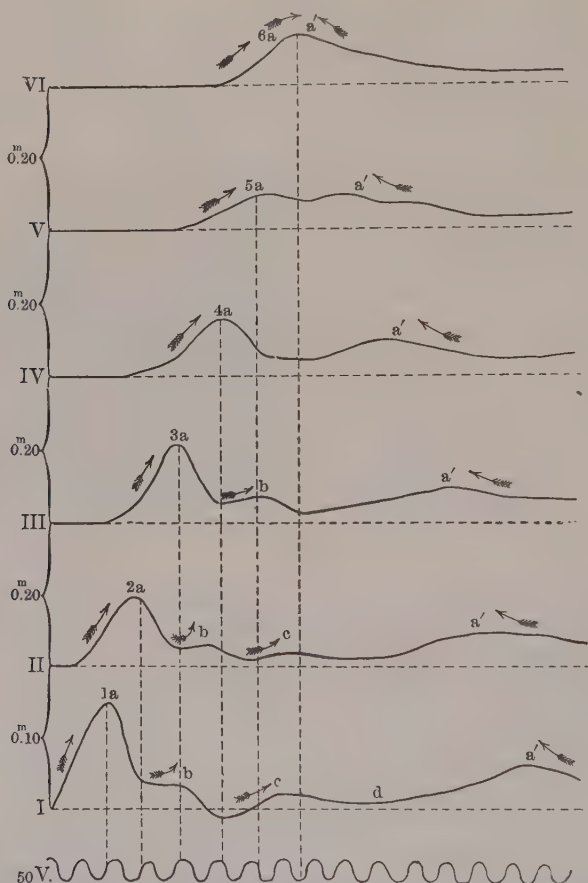
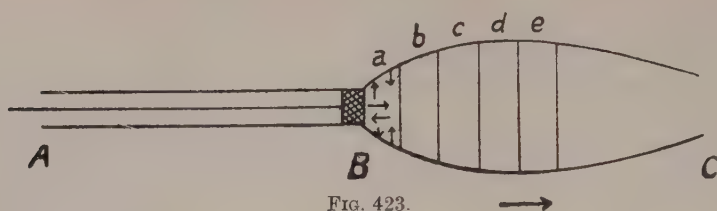


FIG. 424. Pulse Curves described by a series of sphygmographic levers placed at intervals of 20 cm. from each other along an elastic tube, into which fluid is forced by the sudden stroke of a pump. The pulse valve is travelling from left to right, as indicated by the arrows over the primary (*a*) and secondary (*b*, *c*) pulse waves. The dotted vertical lines, drawn from the summit of the several primary waves to the tuning-fork curve below, each complete vibration of which occupies $\frac{1}{50}$ sec., allow the time to be measured which is taken up by the wave in passing along 20 cm. of the tubing. The waves (*a'*) are waves reflected from the closed distal end of the tubing; this is indicated by the direction of the arrows. It will be observed that in the more distant lever (VI) the reflected wave, having but a slight distance to travel, becomes fused with the primary wave, so that the rise of pressure in VI is actually greater than that in V. (From FOSTER, after MAREY.)

with practically no loss of time to all parts of the tube AB. This rapid spread of the wave of pressure applies only to an incompressible fluid within a rigid tube. The pulsation will be retarded if we have an incompressible fluid within a tube whose wall is distensible and elastic. If we imagine (Fig. 423)

an elastic tube BC filled completely with water and connected at B to a rigid tube, which is provided with a piston, the first effect of a rapid movement of fluid driven in by the piston will be a rise of pressure at the point immediately in front of the piston, viz. at *a*. The wall being distensible, and pressure being propagated along the fluid in every direction, the rise of pressure at *a* will be spent partly on the particles of fluid in front of it, viz. at *b*, but also on the walls of the tube, so that this is stretched and the cross section of the tube enlarged. The distended segment at *a* will then exert a pressure on the contained fluid, driving this backwards and forwards. The fluid on its side towards the piston will tend to come to a stop, while that towards the distal end of the tube will be accelerated. The distended wall therefore returns to its original diameter, and the next segment at *b* is stretched in its turn, so that a wave of increased pressure is propagated along the tube in the direction of the arrow.

The velocity with which this wave is propagated depends on the density of the fluid, *i.e.* its inertia, and on the resistance of the walls of the tube to distension, *i.e.* on the rapidity of its recovery. The velocity of propagation of the wave of increased pressure, or the wave of expansion of the artery, is expressed by the following formula :

$$v = k\sqrt{\frac{gea}{Dd}}$$

where *v* is the velocity per second ; *g*, the acceleration due to gravity ; *e*, the elastic coefficient of the wall ; *a*, the thickness of the wall ; *d*, the diameter of the tube ; *D*, the density of the fluid ; and *k*, a constant.

The elastic coefficient *e* of the arterial wall becomes larger as the arterial wall is distended. The velocity of propagation of a wave of pressure in the arterial system will thus be greater when the arterial pressure is high than when it is low.

If the end *c* of the tube is closed, the wave of positive pressure on arriving at *c* will be reflected back as a positive reflected wave. If a tracing be taken of the oscillations or variations of pressure in the tube, two waves at least are seen, one of which is the primary wave due to the movement of fluid caused by the piston ; the other is the secondary wave reflected back from the periphery. That the secondary wave is a reflected one is shown by the fact that the nearer to the peripheral resistance the pulse is recorded, the nearer is the secondary to the primary wave, as is seen in Fig. 424.

If the tube BC be widely opened a reflected wave is also observed, but this time of reversed sign, *i.e.* the wave is one of negative pressure. The production of this wave is dependent on the momentum of the moving column of fluid.

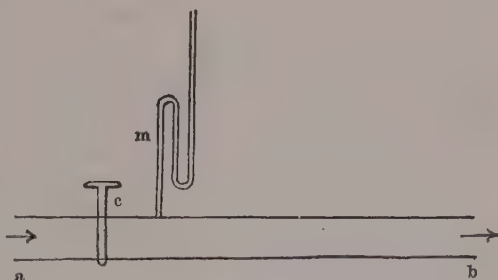


FIG. 425.

If in the tube *ab*, with a tap at *c* and a manometer *m* (Fig. 425), the current of fluid be suddenly checked by turning the tap *c*, the column in front of the tap, having a certain momentum, will tend to go on moving and therefore produce a suction or 'negative pressure' behind it. When a wave of positive pressure arrives at the open end of a tube, there is a sudden increase in the velocity of output, and the momentum of the mass of fluid which is thrown out causes a similar suction or negative pressure, which travels back the whole length of the tube. If the end of the tube is

only partially closed, every primary positive wave will be transformed into a reflected one which is partly positive and partly negative. Since both these reflected waves travel through the tube with the same velocity and will mutually interfere, the result may be either a positive or a negative wave or nothing at all, according to the degree of constriction.

In a branching system of tubes, such as the arterial system, reflection of waves must take place at every division. All the conditions for the origin and interference of such waves are present in the arterial system. It is impossible, however, to say *a priori* whether any reflected wave will form a marked feature on the pulse tracing. It is possible that the multitudinous reflections which must occur in every part of the arterial system may interfere with one another to such an extent that they mutually annul each other. The identity of any secondary wave in the pulse tracing must therefore be determined by exact measurement and experiment.

To study the pulse more fully it is necessary to obtain a graphic record of the expansion of the arteries or, what comes to the same thing, of the

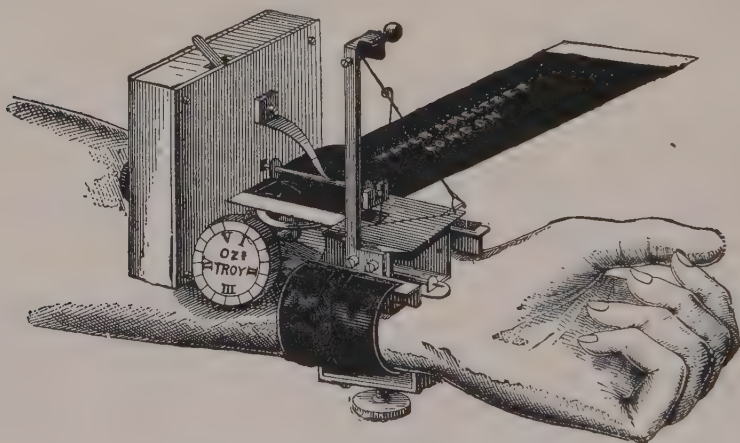


FIG. 426. Dudgeon's Sphygmograph, showing its Mode of Application to the Radial Artery.

exact changes in pressure which produce this expansion. For this purpose a manometer which has very little inertia, such as Wiggers' or Piper's, must be used, or the expansion of the artery may be recorded photographically. The expansion of the artery is approximately registered by means of a lever, which may be made to rest more or less heavily upon the artery, and the movements of which are recorded on a blackened surface. Such an instrument is called a *sphygmograph*. Of the many forms of sphygmographs, Dudgeon's is perhaps the most convenient for clinical purposes.

It is provided with a dial by which the pressure on the artery can be graduated, and has a small clockwork arrangement for moving along the slip of smoked paper on which the records are taken (Fig. 426). The arrangement of the levers in this form of sphygmograph is shown in Fig. 426A, where *r* is the (adjustable) spring, bearing by its button *p* on the artery. The up-and-down movements of *r* are transmitted to *s*, being much magnified and converted into side-to-side movements. The point of *s* rests on the blackened surface represented in section at *A*, and scratches on this, when moving, a magnified record of the expansion of the artery under the knob *p*.

In all such sphygmographs the moving parts have a considerable amount of inertia, so that the curve they give is always more or less deformed. This fact must be borne in mind when comparing the pulse curves obtained by means of a sphygmograph with

those given by the more perfect forms of manometer with optical methods of recording. If an open cup be firmly pressed to the skin over an artery, such as the carotid or sub-clavian, and be connected by a tube with a 'segment capsule,' the excursions of which are recorded photographically, curves may be obtained reproducing in all particulars those given by optical manometers (Fig. 428).

The sphygmograph is generally applied to the radial artery, since this is near the surface and is supported by bone, and the arm is well adapted for the application of the sphygmograph. The pulse curve obtained by means of a sphygmograph varies according to the artery employed and the force with which the lever presses on the artery, but all the curves present the same general features.

The velocity of the pulse can be measured by taking simultaneous tracings from two arteries separated by some distance from one another, such as the femoral artery and the *dorsalis pedis*, or from the carotid and radial arteries. In a healthy individual the velocity varies between 7 and 10 metres per second. The more rigid the arteries the greater will be the velocity, so that the velocity of propagation gradually increases with advancing age, and is higher in the arteries of the lower extremities than in the more distensible arteries of the arm.

The length of the pulse wave can be found by multiplying the velocity of transmission by the time occupied by the wave in passing any given point (0.8 sec.), so that if the velocity of transmission be taken as 7 metres per second, the length of the wave is about 5.6 metres. The pulse wave thus reaches the periphery long before it has been completed in the aorta.

Fig. 427 represents a pulse curve taken from the radial artery by means of a Dudgeon's sphygmograph. The classical type of pulse curve, which this illustrates, shows an abrupt upstroke,



FIG. 427. Pulse Curve from Radial Artery.

the anacrotic limb, or percussion wave, *a-b*, a peak at *b*, and a slower downstroke, or catacrotic limb which is broken by secondary waves, the most conspicuous of these being the *dicrotic wave*, with its preceding *dicrotic notch*, *c*. The usual sphygmogram (Fig. 427) should be compared with the curves, taken by more perfect methods, in Fig. 428, so as to appreciate the deformation by ordinary sphygmographs of the real curve of expansion of the arterial wall.

The general form of the pulse curve varies with changes in the heart, in the arteries and in the peripheral resistance. Thus, some curves may present secondary elevations on the ascending part, and are called *anacrotic*, while in others all secondary elevations occur on the descending part. The latter type is called *catacrotic*, and is the tracing usually obtained from a normal radial artery. By comparing these two types of curves with the corresponding intraventricular pressures, we find that in both cases blood is flowing into the aorta during the whole time from the beginning of the primary elevation to the notch just before the dicrotic elevation. This is shown by the fact that the intraventricular pressure is all this time slightly higher than the aortic pressure. So long as this is the case, blood must flow from ventricle into aorta. (This fact proves that there is normally no part of the cardiac cycle during which the ventricle remains contracted

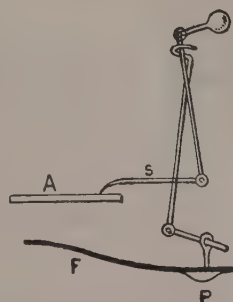


FIG. 426A. Diagram of Arrangement of Recording Lever in Dudgeon's Sphygmograph.

and empty, the ventricle in all cases relaxing before it has completely emptied itself of blood.)

Occasionally the first secondary elevation occurs on the ascending part of the curve, which is then called *anacrotic*. Such a curve is normally seen in the subclavian artery, but in the radial artery usually only in cases of high arterial pressure with an ascending plateau in the intraventricular pressure tracing. When the peripheral resistance is high, or when an extra large amount of blood is thrown into the aorta at each stroke of the heart (*e.g.* by slowing of the rate), the aortic pressure rises very abruptly at the commencement of the ejection phase, and then more slowly so long as blood is flowing in, and we get an ascending systolic plateau and an anacrotic pulse. Hence we obtain an anacrotic pulse in old people with Bright's disease, in whom the peripheral resistance is very high, and also in animals when the heart is slowed by vagus action.

The production of the dicrotic elevation is favoured by any influence which increases the elastic resiliency of the arteries or causes the primary elevation of the pulse to be extensive and sharp. Thus it is much more pronounced in young people than in old people whose arteries have become rigid. When the peripheral resistance is low through relaxation of the arterioles, and the heart is beating forcibly, as in many cases of fever, and also to some extent after a good meal with alcohol, the dicrotic elevation becomes very marked. Under such circumstances it may easily be felt with the finger at the wrist, and in many cases the mistake has been committed of taking the dicrotic wave for a normal beat, and so doubling the rate of the pulse.

It has been suggested that, in the production of such a marked dicrotism, reflection from the periphery may play an important part. With a high blood pressure and rigid arteries, a reflected wave will travel back very quickly and will tend to add itself to the primary wave. With a low blood pressure, dilated arteries, and the output of the heart thrown rapidly into a relatively empty arterial system, the primary wave will rise and fall very rapidly, and the reflected wave will travel back along the arteries more slowly, so that its main effect might be to add to the dicrotic elevation normally proceeding outwards from the heart towards the periphery. The Fig. 424 VI would represent the condition as it is found in the femoral artery under normal circumstances when, according to Frank, the reflected wave adds to the height of the primary wave. In Fig. 424 V the reflected wave 'a' would tend to add to any dicrotic elevation present at this point, and might represent the relation existing in the arterial system with relaxed arteries and a heart beating forcibly, but throwing out only a small amount of blood at each beat.

Considerable differences are observed between the *central* pulse as recorded in arteries such as the subclavian, and the intermediate or terminal pulse given by arteries such as the carotid, radial or dorsalis pedis. These alterations are due to the fact that the contour of the pulse, as it occurs at the aortic arch, is modified in its transmission to the periphery by friction, by incidental vibrations and by interference due to reflected waves. The central pulse, as recorded in Fig. 428 from the subclavian artery, shows the following features:

- (1) An oscillation between A and B, due to the auricular systole.
- (2) A second elevation between B and D which corresponds with the isometric part of the ventricular contraction. (1) and (2) are probably transmitted vibrations.
- (3) At D the semilunar valves open, and blood is rapidly ejected into the aorta, giving the big elevation in pressure, and the main pulse between D and G. The sudden rise of pressure in the aorta sets the column of blood within

the elastic vessel into vibration, giving the overshoot at E and the return wave or anacrotic halt, E F.

(4) The arterial curve now follows the intraventricular pressure (*vide* Fig. 372), the flow of blood continuing quickly up to G, but then slowing off during the rest of the ventricular systole to H (Fig. 428).

(5) At the beginning of ventricular diastole there is a rapid backward movement of the blood towards the heart, causing the *incisura*, H I, and brought up rapidly by the closure of the aortic valves. The rebound of the blood from the valves causes one or two secondary elevations, K, after the *incisura*.

(6) The curve then falls gradually until the next ventricular systole supervenes, sometimes with slower waves at M.

The peripheral pulse gives similar features to the central pulse, but modified by the conditions mentioned above. The preliminary and anacrotic oscillations disappear (though the anacrotic oscillation may be counterfeited by a momentum swing of the lever in the ordinary imperfect sphygmograph); the *incisura* becomes less sharp, and is replaced by the *dicrotic dip*, and the wave K is replaced by the sometimes very conspicuous *dicrotic wave*; the main up-stroke is delayed and its rise more gradual, while the amplitude of the whole curve is usually diminished. These changes are more marked as the periphery is approached, until finally in the smallest arteries and in the capillaries the pulse may disappear altogether.

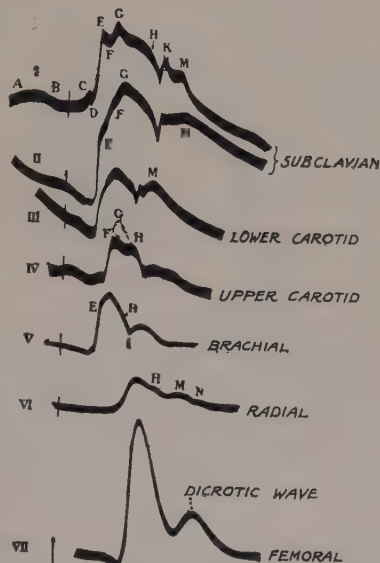


FIG. 428. Pulse Tracings from Arteries, taken by Air Capsules and Optical Recording. (WIGGERS.)

REFLECTED WAVES. It would seem that the pulse curve, as recorded in the aorta and the arterial trunks given off from the aortic arch, can be referred entirely to events taking place in the heart during systole or at the beginning of the aorta at the commencement of diastole; and there is no reason to assume the co-operation of waves reflected from the periphery to explain the production of any of the secondary waves observed on the pulse. The effect of the propagation along an elaborate system of elastic tubes of the sudden wave of pressure started in the aorta must be to diminish the rapidity of onset of each primary wave, and therefore to diminish the secondary vibrations of the curve. In an elastic system of tubes such as the arterial system, there are factors at work analogous in many respects to those responsible for the deformation of the curve given by an imperfect manometer. These would be of two kinds—viz. oscillations of the column of fluid within the stretched arterial wall, and the reflection of waves from different points in the periphery. Many of these reflections will interfere with and annul one another. But in the arterial system there are certain points where distinct reflections of waves can be expected—e.g. in the circle of Willis, at the bifurcation of the aorta into the two iliac arteries, and in the superficial and deep arterial arches in the hand and the foot. We have distinct evidence that such waves are set up and modify the form of the pulse in the femoral and brachial arteries and their branches. Thus in the Fig. 428 V-VII, the primary rise of pressure in the femoral artery is higher than even the primary rise in the subclavian. This condition of things is explicable only on the assumption of a reflected wave passing back along the artery just after the passage of the primary wave, so that the two are summated. In the same way, although the dicrotic depression in the curve (Fig. 428, VII) is no doubt mainly the propagated effect

of the incisure observed in the aortic pulse, it is probably deformed, and the subsequent elevation exaggerated, as a result of reflection of some wave from the periphery. The occurrence of reflected waves may serve to explain why the systolic pressure in the femoral artery is found higher, and the diastolic pressure lower, than in the brachial. The femoral artery being more rigid than the brachial, and the peripheral resistance more definitely localised, reflected waves occur in the artery at so short a time after the primary wave has passed down, that there is summation of the two waves, with production of a higher maximum and a lower minimum than was present in the waves as started in the aorta. If the leg be plunged into hot water, so as to dilate all its arterioles, this difference between the arm and the leg systolic pressures disappears. The varying development of reflected waves on the two sides may also explain why the systolic pressures in the two arms are rarely found to be identical.

A. V. Hill and Bramwell have pointed out that, as the pressure rises rapidly in the artery at each pulse and the wall becomes more rigid, there is a corresponding increase in the velocity of propagation of the wave along the artery which would tend to make the rise steeper towards the periphery. This will be more marked the more rigid the arterial wall, and may account for the primary elevation in the big arteries of the legs being higher than in the more extensible arteries nearer the heart.

From time immemorial the physician has sought by feeling the pulse to come to some idea as to the condition of the circulation. A number of different qualities have therefore been distinguished, *e.g.* the *rate* may be rapid or slow, the size or *amplitude* large or small, while the *hardness* of the pulse is determined chiefly by the blood pressure. If the pulse is compressible it is spoken of as *soft*; if it can only be obliterated with difficulty it is *hard*. Certain combinations of these qualities are also described. Thus a large and hard pulse is spoken of as *strong*, a *weak* pulse being both small and soft. A small hard pulse is called *contracted*. If the rhythm of the heart beat is irregular the pulse is also *irregular*. An *intermittent* pulse is one in which one heart beat is dropped occasionally, *e.g.* once in every four or eight beats, and may be due to the interposition of a ventricular contraction which is too weak to propel the pulse so far as the radial artery, or to the occurrence of an extra beat which is followed by a compensatory pause.

A distinctive pulse is that known as the '*water-hammer*' pulse, which is observed in cases where the aortic valves are injured or diseased so as to allow of regurgitation into the ventricle. The systolic rise of pressure in the arterial system is followed by an extremely rapid fall, so that towards the end of diastole the pressure in the arteries may be insufficient to keep the arterial system filled. Under such conditions, if the arm be held above the head, and the wrist of the patient be grasped, the pulse in the arteries of the wrist is felt as a smart blow coinciding with each beat of the heart.

Judgments as to the conditions of the heart and circulation from the feeling of the pulse must, however, be made with extreme caution. The pulse curve may indeed give approximate information as to the condition both of the heart and the arterial system. Thus, the period between the beginning of the primary elevation and the dicrotic notch corresponds to the outflow of blood from ventricle to aorta. A large pulse curve does not necessarily indicate a big output, since the expansion of the artery is determined not only by events occurring in the aorta but also by the tonus of the artery under the finger and the resistance in the peripheral branches.

THE CIRCULATION THROUGH THE CAPILLARIES

The capillary circulation is most easily studied by examining under the microscope the tongue of the frog or the web of the frog's foot, when a network of vessels is seen, consisting of small arteries, capillaries and veins. The flow of blood in the arteries is rapid, whereas in the veins it is generally

possible to distinguish the individual blood corpuscles. In the capillaries the flow is from arteries to veins, though, on account of the reticular arrangement of these vessels, the direction of the stream through them is not quite constant. If a group of capillaries be watched for some time, the blood may at first hurry through a number of them with great rapidity; the flow then becomes slower and may quicken up to a moderate pace again. These variations in the capillary flow are probably associated with spontaneous alterations in the condition of contraction of the small arteries supplying the group of capillaries. It is easy to observe that the arterial flow is pulsatile, the pulsation disappearing in the capillaries and veins. Another difference between the circulation in these three kinds of vessels is to be found in the condition of the peripheral zone. In the arterioles the blood stream is divided into two parts, the peripheral stream, consisting only of colourless plasma with occasionally a stray leucocyte—and an axial stream, in which all the red blood corpuscles are being hurried along. In the veins there is a similar peripheral plasmatic zone; but here we find regularly scattered leucocytes which travel rather more slowly than the axial stream of red corpuscles. The formation of this axial zone is purely mechanical, and may be imitated in any fluid containing in suspension particles whose specific gravity is somewhat higher than that of the fluid. In the capillaries there is no separation of the two zones, since the lumen of these vessels is so narrow that often the corpuscles, passing in single file, are squeezed out of shape as they progress. The corpuscles are evidently elastic structures, and may be seen to bend if they impinge on the dividing point of two capillaries, before they are finally swept off by the stream into one or the other.

The circulation through the surface capillaries of the skin in man, and in other tissues can readily be observed when a microscopic examination is made by reflected light. The skin is for this purpose covered with cedar oil or liquid paraffin (Fig. 429).

The capillary wall is composed of a single layer of elongated flattened cells which present little resistance to the passage through them by diffusion of dissolved substances. In this way the tissue cells obtain oxygen from the red blood corpuscles and nutriment from the plasma, and give off to the circulating blood carbon dioxide and other effete substances as the products of their metabolism. There is evidence that in many situations the cells forming the capillary wall are contractile, and since contractility seems to be a universal attribute of the capillaries, it must play an important part in determining the amount of blood flow through an organ in accordance with its needs. In resting tissues many of the capillaries are so constricted as to allow of no flow at all.

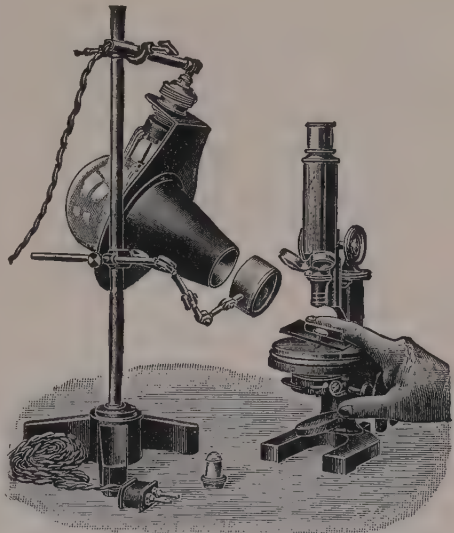


FIG. 429. Arrangement of Illumination for Viewing Skin Capillaries. (From "Recent Advances in Physiology.")

The average length of a capillary is between 0.4 and 0.7 mm. The velocity of blood flow can be directly determined by observing under the microscope the time taken by any given corpuscle to travel a measured distance on the microscope stage. The mean velocity determined in this way varies from about 0.5 to 0.8 mm. per second.

The blood pressure in the capillaries may be measured approximately by applying pressure to the outer surface of the skin or mucous membrane by means of a Recklinghausen capsule (Fig. 411) and noticing the point at which blanching of the surface commences. The errors of this method are considerable. The pressure in the capillaries, as found by this method, is low, and necessarily varies with the position of the part under investigation, *i.e.* with the hydrostatic pressure. It is raised, often greatly, when there is a dilatation of the arterioles, and lowered when these constrict. Experiments by Leonard Hill have shown that the capillary pressure is not often as high as has been previously supposed, and often lies between 0.5 and 6 cm. water.

Capillary pressures have also been measured in man by Carrier and Rehberg as follows: A fine glass capillary is filled at the point with saline solution and pushed into a skin "capillary" which is under observation under the microscope. Attached to the other end of the capillary tube is a water manometer, by means of which a definite pressure is applied to the column of saline solution in the capillary glass tube. When the blood capillary is pierced, blood will flow into the glass capillary if the capillary pressure is higher than that in the water manometer; if lower, no blood will enter; if the same, blood will pulsate in and out of the glass capillary at each heart-beat.

In man it has been found that the capillary pressure in the hand varies with the position of the hand with reference to the heart, and may be as great as 30 cm. water, or as little as 4 or 5 cm.; but, however high up the hand is placed, it never falls below a certain level, of about 4 to 5 cm. The reason for this is because the veins collapse down and restrict the flow when the hand is held in such a position that the venous pressure becomes negative. The capillary pressure is thus always maintained at a positive value, which varies according to the position. In the feet the capillary pressure is normally prevented from attaining very high values, owing to the presence of valves in even the smallest veins, and to the occurrence of constant small muscular movements, which, by forcing the blood into these veins, enables them to act as a kind of pump.

Owing to the fact that a varying resistance—that of the arterioles—lies between the capillaries and the arteries, the pressure in the capillaries must stand in much closer relationship to that in the veins than to that in the arteries. One cannot therefore argue that a fall of arterial pressure necessarily involves a fall of capillary pressure in all parts of the body. We can only judge of changes in the capillary pressure by simultaneously taking the pressures in both the afferent and efferent vessels. If these both rise or fall together we may be certain that the capillary pressure also rises or falls. When the arterial and venous pressures move in opposite directions, it is difficult to say what alterations, if any, will be produced in the capillary pressure.

The resistance to the flow of blood through the capillaries is determined by the internal friction, *i.e.* the viscosity of the blood; this varies in different animals between three and five times that of water. The chief seat of the resistance in the vascular system is in the arterioles, and it is in this region that the chief fall of pressure occurs.

No part of the circulation shows greater variations than the capillary system. We must think of this as a vast irrigation system of canals—the greater part of which are closed under normal circumstances, and

open only when the tissue requires a large increase in the supply of blood. In muscle the capacity of this irrigation system may be increased 750 times during activity. It seems probable that such changes will affect arterial pressure by their influence on the total capacity of the vascular system (if of wide enough occurrence) as well as by alterations thereby produced in the peripheral resistance.

THE FLOW OF BLOOD IN THE VEINS

In the veins there is a constant decrement of pressure as we pass from the periphery towards the heart. Owing to the fact that no appreciable resistance lies between the veins and the heart, the difference of pressure necessary to maintain a constant flow through these vessels is very small. Thus, in the horizontal position, the pressure in the femoral veins may be from 5 to 10 mm. Hg., and in the inferior vena cava from 1 to 5 mm. The pressure in the great veins near the heart is generally negative owing to the aspiration of the thorax, and this negative pressure is naturally increased during inspiration. Opening the thorax, therefore, causes a rise of pressure in all the large veins. In the latter, the pressure is lowered by vigorous action of the heart

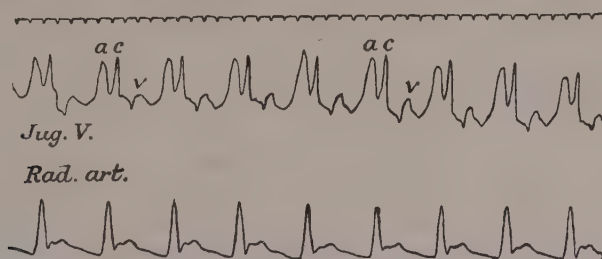


FIG. 430. Venous Pulse Tracing from Jugular Vein compared with the Arterial Pulse Tracing from the Radial Artery.

pump and raised when this fails in any way. In the peripheral veins the pressure is more dependent on the flow through the corresponding arteries. If an artery of a limb be ligatured, the pressure in the small veins of the limb sinks until it is reduced to the pressure in the nearest large trunk in which a flow of blood continues.

Each cardiac cycle causes variations in the pressure in the great veins next the heart in two ways :

(1) By the transmission along the veins of the alterations in the intra-auricular pressure.

(2) By the diminution in the volume of the heart in consequence of the expulsion of its blood along the arteries with each heart beat.

On this account the jugular veins show pulsations with each heart beat which are somewhat complex in character and resemble closely those occurring in the auricle (*vide* p. 720). In Fig. 430 a tracing from the wall of the jugular vein is given. It will be seen that each heart beat gives rise to three variations in pressure within the veins. These three undulations are evidently exactly analogous to those given in Fig. 372 as occurring in the auricular tracing. We should therefore regard *a* as the auricular contraction, *c* as the elevation due to the closure of the auriculo-ventricular valves, *v* as the elevation due to the accumulation of blood in the auricles during the ventricular systole. The curve *c* is probably due in part also to an impact transmitted from the great arterial trunks to the intrathoracic veins. These

venous pulsations are much more marked in cases of heart disease, where there is partial failure of the heart pump and overfilling of the venous system, often combined with incompetence of the auriculo-ventricular valves.

Besides the favourable influences exercised on the circulation through the veins by the aspiration of the thorax, a considerable part is played in the venous circulation by the emptying of the veins by pressure upon their walls. The adjuvant effect of passive or active movement on the circulation through the veins is rendered possible by the existence in these vessels of valves, which are semilunar folds of the intima projecting into their lumen, and so arranged that they allow the passage of blood only towards the heart. Two such valves are, as a rule, situated opposite to each other. Every movement of a limb, active or passive, causes an external pressure on the veins and therefore empties them towards the heart. Thus in walking, each time the thigh is moved backwards the femoral vein becomes empty and collapses, and fills again as soon as the leg is brought forward to its former position. When muscular movements become general, as in walking or running, the active compression of the veins thus brought about plays an important part in hurrying the blood into the right heart, so that the output of this organ is increased.

Since the blood in the vessels is subject to the influence of gravity, we should expect to find that the pressure in the veins of the foot was equal to the pressure in the veins, say, of the hand at the level of the heart *plus* the pressure equivalent to the column of blood between these veins and the heart, *i.e.* about a metre of blood, but on measuring the pressure in these veins, this is found not to be the case. The pressure, indeed, in the veins of the foot is but little higher than that in the veins of the hand, as L. Hill has shown. When a man assumes the upright position, the arteries of the leg and foot contract until, under the combined influence of the heart's contraction and gravity, the blood supply to the capillaries is just adequate. The return of the blood from the dependent parts cannot be ascribed entirely to the heart beat, but is largely due to the contractions of the muscles of the limb, which press on all the deep and superficial veins, and in virtue of the valves force the blood contained therein past Poupart's ligament into the abdomen. This explains why it is so difficult to stand for any length of time without moving, and emphasises the need of moderate exercise for the maintenance of a normal circulation.

THE NERVOUS CONTROL OF THE BLOOD VESSELS

Every organ of the body requires an increased blood supply during activity, which means that blood must be diverted from the inactive to the active tissues. All parts of the body co-operate in subordination to the activity of that tissue whose function for the time being is of the greatest importance to the organism. This subordination of the part to the whole is chiefly effected through the central nervous system, though local and chemical mechanisms also play some part in the process.

Our knowledge of the nervous control of the blood vessels dates from the discovery, by Claude Bernard, that nerve fibres maintain them in a state of tonic constriction. Bernard showed that if, in the rabbit, the cervical sympathetic on one side be divided, the vessels in the corresponding ear dilate. Vessels come into prominence which were previously invisible, and on account of the greater flow of blood thus produced, the ear on the side of the section becomes warmer than the normal ear. If the head end of the divided

sympathetic nerve be stimulated, all the vessels of the ear contract, and the ear becomes colder than that of the other side. The fact that the dilatation of the vessels is produced by section of the cervical sympathetic and lasts for a considerable time after any irritant effect of the section must have passed off, shows that the ear vessels are *continually* under the influence of tonic constrictor impulses arising in the central nervous system and proceeding to them along the nerve fibres of the cervical sympathetic.

The paralysis of the ear vessels, though lessening the resistance to the flow of blood there, affects too small a vascular area to have any marked influence on the general arterial pressure. If the spinal cord be divided on a level with the origin of the first dorsal nerve, or higher, a wide area is affected and the blood pressure sinks considerably. In the dog it may fall from 120 mm. Hg. to 40 or 50 mm. Hg. The heart after the section beats more rapidly than before, so that the fall of pressure must be ascribed to a change affecting the blood vessels and lowering the resistance to the flow of blood. Since a maximal effect on the blood pressure is produced by section of the cord at this level, one may conclude that the tonic constrictor impulses to all the vessels of the body pass through this segment of the cord before leaving it to be distributed to the arterial walls.

The source of these impulses may be made out by studying the effect of sections through different levels of the nervous system. Division of the cord at, or below, the second lumbar nerve causes no effect on the blood pressure. On making a section above the first lumbar nerve, the effect produced increases progressively until the first dorsal roots are reached, where it is maximal; stimulation of the lower end of the cut dorsal cord causes widespread vascular constriction and a large rise of blood pressure. Section of the crura cerebri, or of the brain stem at the upper border of the fourth ventricle, leaves the blood pressure unaffected. Destruction of a small region of the medulla situated on each side of the middle line in the neighbourhood of the facial nucleus, *i.e.* in the forward prolongation of the lateral columns, after they have given off their fibres to the decussating pyramids, causes an immediate and maximal lowering of the blood pressure.

We must therefore conclude that all the vessels in the body are kept in a state of tonic contraction by impulses arising in this portion of the medulla oblongata, travelling down the cord as far as the dorsal region, and then passing out of the cord by the dorsal and upper lumbar nerves. This conclusion is confirmed by the fact that, whereas stimulation of the anterior roots of the cervical, lower lumbar and sacral nerves has no influence on the blood pressure, a rise of arterial pressure can be obtained by stimulating any of the anterior roots from the first or second dorsal to the second or third lumbar. The same effect is produced by stimulation of the white rami communicantes from these roots to the sympathetic system, by excitation of the sympathetic system itself, or of the splanchnic nerve.

THE VASOMOTOR CENTRE. The portion of the medulla concerned with the sending out of the tonic vasoconstrictor impulses is spoken of as the vasomotor centre. This is played upon by afferent impulses from the higher centres of the brain, and especially by afferent impulses travelling from all parts of the body, including those carried by the vagi from the viscera of the chest and abdomen. Whether in the absence of all afferent stimuli the centre would be active is doubtful; all we know is that the sum of the stimuli arriving at the centre produces a state of average continued activity, which is responsible for the maintenance of arterial tone.

An important factor for the maintenance of the tonic activity of the centre is the presence of carbon dioxide in the blood. If this be lowered by

forcible ventilation of the lungs, so as to remove much carbon dioxide out of the blood, a profound fall of blood pressure occurs owing to paralysis of the vasomotor centre. On the other hand, anything which interferes with the gaseous exchanges of the centre, whether obstruction to respiration, absence of oxygen in the air breathed, the action of cyanide, or a failure of the blood supply, as by ligature of the cerebral arteries, calls forth an increased state of activity of the centre. This can be best studied by observing the changes in the blood pressure produced in a curarised animal by the cessation of artificial respiration.

These changes depend partly on the stimulation of the vasomotor and vagus centres by the venous blood, and partly on the affection of the heart itself. We will first consider them with both vagi cut. For several seconds after leaving off the artificial respiration the only change noticed is

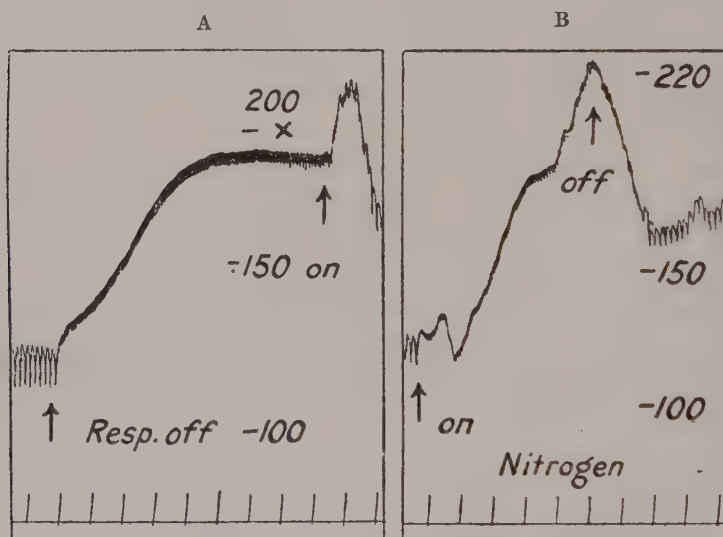


FIG. 431. Blood Pressure Changes in a Cat. (MATHISON.)

A. After cessation of respiratory movements.

B. As a result of artificial respiration with nitrogen.

the absence of the respiratory oscillations. Sooner or later the blood pressure suddenly rises rapidly (Fig. 431 A) and in another ten seconds may reach a height twice as great as it was previously. The heart beats a little more forcibly, but its frequency is almost unaltered. The blood pressure remains at this height for about a minute and then gradually falls, the heart beats becoming smaller and smaller until the pressure has sunk almost to zero. *This fall in pressure is due to the failure of the heart.* The heart gets overfilled, heart block ensues, and it gradually loses the power of expelling any of its contents. The vessels, however, remain constricted until the death of the animal. This is shown by two facts. If, while the pressure is sinking, artificial respiration be recommenced, the heart, supplied with oxygen, at once begins to beat more forcibly, and the blood pressure may rise to an even greater height than immediately after the commencement of the asphyxia. Again, if the volume of the kidney be recorded by means of the oncometer, the rise of general blood pressure produced by asphyxia is seen to be accompanied by a rapid shrinking of the kidney, and this shrinking endures until

the animal dies, showing that the fall of blood pressure following the rise is due, not to a giving way of the arterial resistance, but to failure of the heart.

Similar results are obtained when the vessels to the brain are ligatured, or when the animal has to respire an indifferent gas free from oxygen, such as nitrogen (Fig. 431 B) or if the oxygen usage of the tissues be suspended by the administration of small doses of cyanide. In the uncurarised animal, the rise of blood pressure is associated with increased respiratory movements and finally with convulsive spasms which may involve practically every muscle of the body.

We have spoken above of the phenomena of asphyxia as being due to the circulation of venous blood. There are, however, two factors which may be concerned, and which may influence the medullary centres and the heart. When the renewal of the lung ventilation is stopped, the increasing venosity of the blood involves a diminished percentage of oxygen and an increased percentage of carbon dioxide; and when asphyxia is excited by cessation of the circulation through the medullary centres, these centres may suffer at the same time from lack of oxygen and from the accumulation of carbon dioxide. The question arises whether one or both of these factors are concerned. It is easy to investigate the action of each separately. A pure oxygen lack may be brought about by allowing an animal to breathe some inert gas, such as nitrogen, or by injecting small amounts of cyanide into the blood; while the effects of accumulation of carbon dioxide in the blood and tissues may be produced by the administration of mixtures containing excess of oxygen, with varying percentages of carbon dioxide. In the first case, not only will the oxygen supply be reduced, but the tension of the carbon dioxide

in the blood will also be kept below normal; in the second case, while the CO_2 tension is raised, the tension of oxygen in the blood will also be kept above normal. In order to obtain results uncomplicated by the influence of anaesthetics, the experiments may be carried out in animals which have been deprived of consciousness by decerebration. Mathison has shown that both with absence of oxygen and excess of carbon dioxide, conditions may concur in the production of the rise of blood pressure in asphyxia. In Figs. 431 and 432 the rise of arterial pressure produced by a short period of asphyxia is compared with that produced by oxygen lack, and by a surplus of carbon dioxide. There are certain minor details in these curves which are of interest. When the oxygen of the lungs is rapidly washed out with a neutral gas, the rise comes on about half a minute later than it would with pure asphyxia. In the latter case it seems

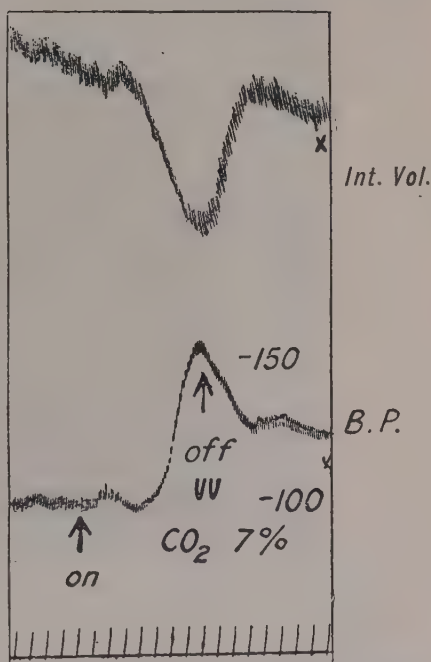


FIG. 432. Tracing of Arterial Blood Pressure and of Intestinal Volume, to show the Influence of a Moderate Increase in the CO_2 tension of the Blood. (MATHISON.)

that the first rise is due to the accumulation of carbon dioxide. The rise under nitrogen, however, when it occurs, is extremely abrupt, and the subsequent fall of blood pressure, *i.e.* the heart failure, is earlier in onset and more rapid than with ordinary asphyxia. When excess of carbon dioxide is administered, *i.e.* 5 to 10 per cent., a marked rise of pressure occurs which is almost entirely conditioned by stimulation of the vasomotor centres and resulting constriction of the peripheral arterioles. If a loop of intestine be placed in a plethysmograph, it will be seen that the rise of pressure coincides with a shrinkage in volume of the intestine, pointing to a vascular constriction (Fig. 432). The rise of blood pressure due to the vascular constriction may be maintained for a considerable period, *e.g.* ten to fifteen minutes, and we do not get the rapid failure of the heart that is observed in an ordinary asphyxia tracing. If partial oxygen lack, or abnormally increased tension of carbon dioxide, be continued for some time, a state of narcosis or paralysis finally ensues, which affects not only the higher centres but also those of the

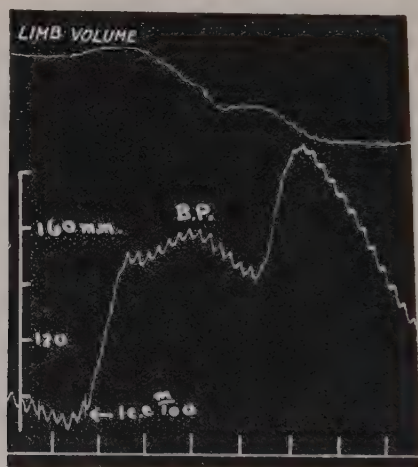


FIG. 433. Decerebrate Cat. Vagi divided. Upper tracing = limb volume. Second tracing = arterial pressure. Lower tracing = time (10 secs.). Injection of 1 c.c. of $\frac{m}{100}$ NaCN into femoral vein. (C.L.E.)

medulla, so that death may result without convulsions or excessive rise of blood pressure.

The action of cyanide resembles that of nitrogen breathing in its main features, but differs from it in having a more rapid onset, and a slower recovery. This is shown by Fig. 433, which also illustrates another feature of asphyxia. The blood pressure curve shows a second rise; this is abolished if the suprarenals are removed: it is due to the liberation of adrenaline into the blood stream, which constantly happens in asphyxia.

Is there any common factor in the two conditions of oxygen lack and carbon dioxide excess, which may account for the similarity in their effects? It has been shown that, whenever there is a deficiency of oxygen, the metabolism of the tissues undergoes alteration, so that the lactic acid formed is not removed by oxidation. Oxygen lack, therefore, is often regarded as synonymous with the production of lactic acid. Lactic acid introduced into the blood stream also causes a rise of blood pressure similar to the asphyxial rise. When the cells of the vasomotor centre are deprived of oxygen, through lack of sufficient oxygenated blood, or are prevented from

using it, as by cyanides, it is probable that they themselves produce lactic acid, which, like carbon dioxide, raises the H-ion concentration of their contents, and thus excites them.

If in the dog, and to a less extent in other animals, the vagi be left intact, the blood tracing during asphyxia has quite another appearance. In this case, there is at first only a slight rise of pressure, but the heart begins to beat very slowly. This slow beat is due to the action of the vagus centre, and is at once abolished by section of the two vagi. The sparing of the heart by means of this vagus action enables it to last longer, so that heart failure comes on rather later than when the vagi are divided. In the increased vagus action,

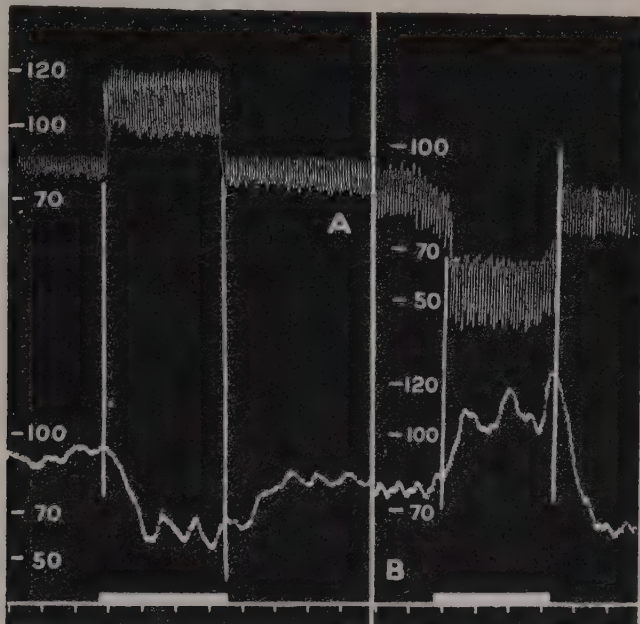


FIG. 434. Blood Pressure Tracings to show Influence of Changes in the Circulation through the Brain on the Activity of the Vasomotor Centre.

The brain was supplied with blood from a separate heart-lung preparation. The upper curve is the pressure in the head (*i.e.*, in the vasomotor centre), which is controlled by the experimenter. The lower curve is the pressure in the vessels of the trunk, which is controlled by the vasomotor centre. In A, a rise of pressure in the head causes vasodilatation and a fall of pressure in the trunk. In B, a fall of pressure in the brain arteries has the reverse effect on the animal's own circulation. (ANREP and STARLING.)

which occurs during asphyxia, two factors are probably involved. The cardio-inhibitory centre in the medulla partakes of the general excitation of the medullary centres, due in the first place to carbon dioxide excess, in the second to oxygen lack. More important is the direct action of the rise of blood pressure on the vagus centre, which has already been described (page 755).

The vasomotor centre, which is so sensitive to the acid metabolites produced by its own activity, has the power of regulating its blood supply according to its needs. If the brain be supplied with blood by means of a circulation distinct from that of the rest of the body, it is found that any rise of pressure in the arteries of the brain, and consequent increased blood supply, brings about the inverse change in the arteries of the rest of the body—so that rise of pressure in the brain vessels means a fall of pressure in other parts of the body, and *vice versa* (Fig. 434).

According to Heymans this phenomenon, like the reflex cardio-inhibition which accompanies it, is a reflex from the *sinus caroticus*, akin to the effects mediated by stimulation of the depressor (*v. p.* 753), and is not a consequence of the effect of pressure on the brain itself.

When the arterial pressure is high, waves are often observed on the blood-pressure curve. These are of two kinds. In completely curarised animals we may observe oscillations of blood pressure corresponding with the respiratory rhythm before the administration of curare, or if the vagi are cut, presenting a rhythm similar to that usual in animals with divided vagi. They are certainly due to irradiation of impulses from the excited respiratory centre to the vasomotor centre in the medulla. In fact, if the curarisation is not complete, a slight twitch of the diaphragm, insufficient by itself to have any mechanical influence on the circulation, may be observed to accompany each rise on the blood-pressure curve. Besides these curves, others are occasionally seen which must arise in a slow rhythmic variation of the constrictor impulses sent out from the vasomotor centre. These waves are known as the Traube-Hering waves and are much slower in their rhythm than the respiratory waves. They are observed, not only during asphyxia, but may occur in blood-pressure tracings from normal dogs, and are frequent in dogs poisoned with morphia. Fig. 435 represents such a tracing taken immediately after cessation of the artificial respiration, and shows only the heart beats and the Traube curves. The presence of these waves may generally be ascribed to a state of abnormal excitation of the vasomotor centre. This excitation may arise in various ways. A very frequent cause is the one just described, *viz.* increased venosity of the blood supplied to the centre. Well-marked Traube curves are often observed in cases of hæmorrhage. In spite of the loss of blood, the vasomotor centres

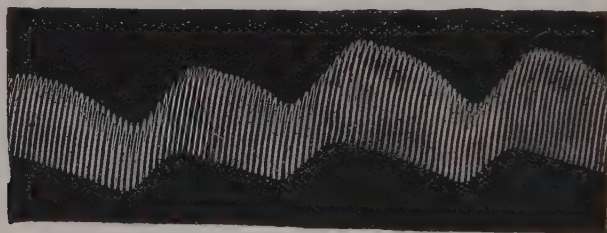


FIG. 435. Blood Pressure Tracing showing Traube-Hering Waves. (C. J. MARTIN.)

maintain a normal arterial blood pressure by means of vascular constriction. As the bleeding continues, this means becomes inadequate, and at this point the 'efforts' of the centres take on a rhythmic character, giving well-marked Traube curves, just as the arm of a man holding up a weight begins to shake before he is obliged to give way through fatigue. If the bleeding still continues, the pressure sinks steadily and the curves disappear.

SPINAL VASOMOTOR CENTRES

The great fall of blood pressure observed after section of the cervical cord is not permanent. After a short time (especially in the cat), the pressure begins to rise, and if the animal be kept alive, may attain a height equal to that found in normal animals.

If the spinal cord of such an animal be destroyed, the blood pressure sinks practically to zero, because the animal has been, so to speak, bled into its own dilated blood vessels. In addition to the chief vasomotor centre in the medulla, there is a series of subsidiary centres in the spinal cord, centres which we may probably locate in the portions of grey matter situated in the lateral horns of the cord and giving origin to the fibres which go to make up the white rami communicantes. By means of these spinal centres a certain degree of adaptation of the blood supply to the various parts of the trunk is possible. The important co-ordination between the state of the blood vessels and the condition of the central pump, the heart, is however wanting, since the blood vessels are now cut off from the cardiac centres, and from that

part of the central nervous system which receives the afferent impulses carried by the vagi.

The spinal centres, like the chief vasomotor centre, are susceptible to changes in the composition of the blood supplied to them. If an animal be kept alive by means of gentle artificial respiration after division of the cord just below the medulla, the blood pressure soon resumes a normal level. If artificial respiration be now discontinued the asphyxia excites the centres of the cord, and the pressure rises. Conversely, if the artificial ventilation be made excessive (acapnia), the blood pressure rapidly falls, but is speedily restored if ventilation, at the same excessive rate, be carried on with air containing 5 per cent. carbon dioxide, or with expired air (Fig. 436). After destruction of the spinal cord, these effects disappear. The spinal centres are also excited by lack of oxygen. There is a difference between the sensibility of the spinal centres to these substances as compared with the medullary centres. Here, as in the medulla, the common factor is probably increased

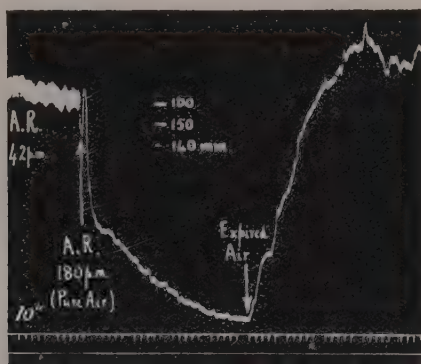


FIG. 436. Effect of Excessive Ventilation on Spinal Cat. Cord cut at second cervical level. With light artificial respiration (42 p. min.) the pressure is 160 m.m. Hg; this rapidly falls on ventilation at 180 p. min., but is restored by respiration, at 180 p. min., with expired air. (DALE and LOVATT EVANS.)

H-ion concentration, the excitation threshold for the medullary centres being lower than that of the spinal centres.

The local spinal centres are connected with the medullary vasomotor centre on each side by tracts of nerve fibres which descend in the lateral columns of the cord.

THE PERIPHERAL TONE OF THE BLOOD VESSELS. Division of the sciatic nerve causes an immediate dilatation of the vessels of the lower limbs, in consequence of their severance from the tonic activity of the vasomotor centres. This dilatation passes off in a day or two, and the vessels acquire a tone, *i.e.* remain in a state of average constriction, which can be increased or diminished by local conditions. This recovery of tone has been ascribed by many physiologists to the existence of a third set of nerve centres in the walls of the arteries. In the absence of any direct histological evidence of the existence of such centres, it seems more rational to ascribe the tonus to the automatic activity of the muscular fibres themselves, aided perhaps by the presence of some substance in the blood.

THE COURSE AND DISTRIBUTION OF THE VASCULAR NERVES

Since the plain muscle of the blood vessels exhibits an automatic tonus, complete nervous control of these tubes can be secured only by the provision of two sets of nerves: one set—constrictor or motor—which will

increase the state of constriction of the vessels; another set—inhibitor or dilator—which will diminish the tone of the arteriole muscle, and cause vascular dilatation.

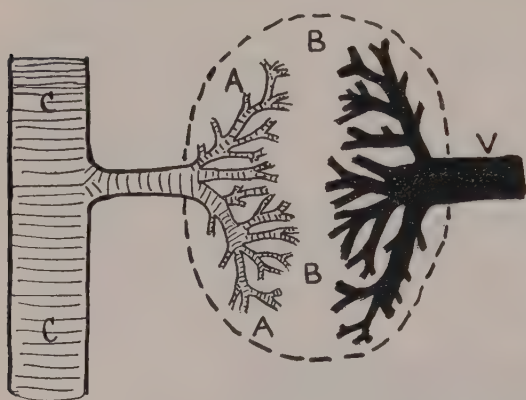


FIG. 437.

Our knowledge of the existence of this second class of nerve fibres to the vessels we owe also to Claude Bernard, who observed that stimulation of the chorda tympani nerve not only evoked secretion from the submaxillary gland, but also increased the blood flow through its vessels five or six fold. Subsequent researches have revealed the fact that nearly all the vessels of the body receive vasoconstrictor fibres, and that many receive also vasodilator fibres. In order to determine the course and distribution of the vascular nerves, it is necessary to have means at our disposal for investigating the condition of the blood flow through different parts and organs of the body. Let us see what effects will ensue on the local circulation, by constriction or dilatation of the arterioles with which it is supplied. If the arterioles *A* in the organ *B* dilate (Fig. 437), the first effect is a diminution of the resistance to the flow of blood into the capillaries beyond. Supposing that the arterial pressure in the trunk *C* remains constant, a local diminution of resistance in *A* will at once determine an increased flow of blood through the arterioles, and a rise of capillary pressure. If the organ is distensible and elastic, the increased pressure in the arterioles and capillaries will cause dilatation of these vessels, and a consequent dilatation of the whole organ. The same effect on intracapillary pressure, and therefore on the volume of the part, may be caused by obstruction to the flow of blood from the veins. But provided that the general blood pressure in *C* remains constant, dilatation of an organ, *accompanied by an increased blood flow through it*, may be taken as an expression of vasodilatation in the arteries with which it is supplied.

We can therefore use the following criteria for the occurrence of a vasodilatation in the arterial supply to any part or organ :

(1) If the surface of the part is translucent, the increased filling of the capillaries will cause redness or blushing.

(2) The increased size of the vessels will cause an *increase in the volume* of the organ concerned.

(3) An increased velocity of blood flow will, if the part be normally below the temperature obtaining in the central organs of the body, raise its temperature, and vasodilatation can thus be detected by the application of the hand or of a thermometer.

(4) Any of the methods mentioned in a previous chapter may be used to determine the velocity in the arteries going to the part, and an increased velocity may be interpreted as due to vasodilatation.

(5) The increased flow through the part may be detected by cutting the main efferent vein and measuring the total volume of blood which flows from it in a given time.

Of these methods the two most used are those based on determination both of the volume of the part, and of the venous outflow from the part. A fallacy may arise, however, unless means be taken to ensure that the general arterial pressure remains constant during the experiment. A rise of general blood pressure will cause a passive expansion of the vessels and of the part supplied, and also increased velocity of blood flow through the part. In all cases, therefore, where it is desired to investigate the conditions of the local circulation, it is necessary to record the general blood pressure. We may take as an instance an experiment on the blood supply to the kidney.

For this purpose we may use a kidney plethysmograph.

Schafer's plethysmograph (Fig. 438), which can be adapted to almost any organ of the body, is made of vulcanite * previously moulded to the size of the organ whose volume is the object of investigation. In one side of the box a depression is left sufficient to accommodate easily the vessels, nerves, or ureter going to the organ. The oncometer is covered with a glass lid which is made air-tight by means of vaseline, the space between the lid and the vessels being also packed with cotton-wool and vaseline. A glass tube is fixed into one corner of the plethysmograph and leads to a piston recorder. Every variation in the volume of the organ causes a movement of air into or out of the oncometer and thus gives rise to a corresponding movement of the recording lever.

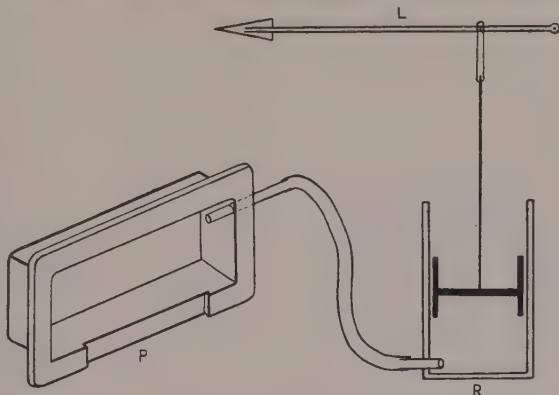


FIG. 438. Diagram of Schafer's Air Plethysmograph.

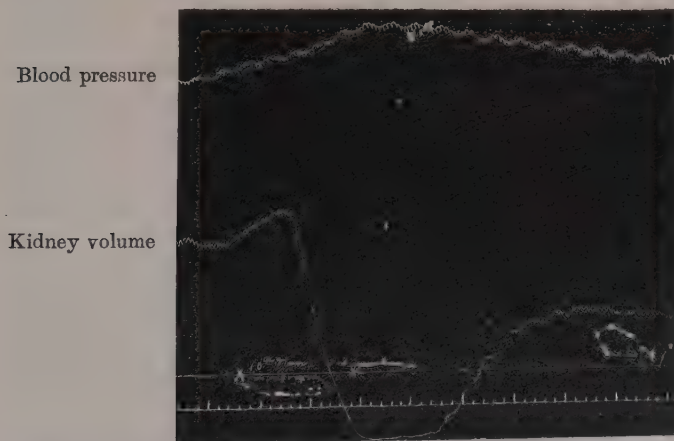


FIG. 439. Simultaneous Tracings of Carotid Blood Pressure and Volume of Kidney. Between $\times$ and $\times$ the peripheral end of the divided tenth dorsal nerve was stimulated. Time-marking = seconds. (BRADFORD.)

The kidney being placed in some such apparatus, and the arterial pressure being recorded, two tracings are obtained at the same time. In the Figure given (Fig. 439), the upper curve represents the carotid blood pressure, while

* A very good material for this purpose is 'Stent's composition,' used by dentists for taking a mould of the jaw in fitting artificial teeth.

the lower is the tracing of the kidney volume. The peripheral end of the anterior root of the tenth dorsal nerve was excited by means of an interrupted current at the point marked with a cross on the tracing. This stimulation was followed by a rise of blood pressure together with a diminution in the kidney volume. The increased blood pressure would by itself tend to force more blood into the kidney and so increase its volume. The fact that the kidney volume diminished shows that there must have been active contraction of the arterioles of the kidney, emptying this organ of blood and so causing it to decrease in size. This contraction of the vessels would tend to cause a rise in general blood pressure and must have taken some part at any rate in the rise actually observed. If the plethysmograph had been used alone, it would have been impossible to determine whether the shrinkage of the kidney might not be due to a lowering of general blood pressure, in consequence of vasodilatation occurring elsewhere, or in consequence of the failure of the heart's activity. On the other hand, without the volume record it would have been possible to determine only that there was increased peripheral resistance somewhere or other in the body.

Instead of taking the volume of the kidney, we might have determined the blood flow through its vessels.

The direct determination of the venous outflow is not well adapted to large organs, on account of the very rapid loss of blood which occurs through the open vein. The method is, however, of great value in dealing with the circulation through small organs, such as the submaxillary glands. In such a case it is usual to hinder or prevent the clotting of the blood by the preliminary injection of heparin, and then, after placing a cannula in the efferent vein of the organ, to allow blood from the cannula to flow into an automatic registering apparatus.

COURSE OF THE VASOCONSTRICTOR FIBRES.—In investigating the course of the vasoconstrictor fibres we have to determine :

- (1) The origin of the fibres from the central nervous system ;
- (2) The course of the fibres on their way to their peripheral distribution in the blood vessels ;
- (3) Their connections with nerve cells.

The first two details can be found by stimulating various nerves and nerve roots in different parts of their course, and observing the effects produced on the local and general circulation. The importance of the third heading is due to the fact that the vascular nerves, like the visceral nerves generally, do not have their last cell station in the spinal cord. The fibres carrying vasoconstrictor impulses, on leaving the cord, do not pass direct to the blood vessels, but come to an end in a collection of ganglion cells, which may belong to the main chain of the sympathetic, or be situated more peripherally and belong to the group of collateral or peripheral ganglia. These fibres, as they leave the central nervous system, are small medullated nerves. They end in the ganglion by arborising round ganglion cells, whence a fresh relay of non-medullated fibres starts and carries the impulses on to the muscle fibres of the blood vessels.

The discovery of the ganglia, with which any given set of nerve fibres is connected, is rendered easy by the use of nicotine (Langley). The first effect of the drug is a powerful stimulation of the ganglion cells, so that, if the drug be injected, there is an enormous rise of blood pressure, owing to the universal vasoconstriction that is produced. The stimulation gives place to a condition of paralysis ; the blood pressure falls below normal, owing to the cutting off of the peripheral vascular nerves from the vasomotor centre. Stimulation of the pre-ganglionic fibres is now without effect, although the normal results follow stimulation of the post-ganglionic non-medullated fibres.

By these methods it has been determined that all the vasoconstrictor nerves of the body leave the spinal cord by the anterior roots of the spinal nerves from the first dorsal to the third or fourth lumbar inclusive. From the roots they pass by the white rami communicantes to the ganglia of the sympathetic chain lying along the front of the vertebral column. Here they take different courses according to their destination.

The fibres to the head and neck leave by the first four thoracic nerves, pass into the sympathetic chain through the ganglion stellatum and ansa Vieusseni to the inferior cervical ganglion, and up the cervical sympathetic trunk to the superior cervical ganglion. Here they end, and the impulses are carried by a fresh relay from cells in this ganglion, and travel as non-medullated fibres on the walls of the carotid artery and its branches.

The constrictors to the fore limb in the dog leave the cord by the white rami of the fourth to the tenth thoracic nerves. The fibres run up the sympathetic chain to the stellate ganglion, where they all end in *synapses* round the cells of this ganglion. The impulses are carried on by non-medullated fibres along the grey rami of the sympathetic to the cervical nerves which make up the brachial plexus, and run down in the branches of this plexus to be distributed to the vessels of the fore limb.

The constrictor impulses to the hind limb in the dog arise from the nerve roots between the eleventh dorsal and third lumbar roots. All the fibres end in connection with cells in the sixth and seventh lumbar and first and second sacral ganglia of the sympathetic chain, whence the impulses are carried by grey rami to the nerves making up the sacral plexus.

The most important vasomotor nerve of the body is the *splanchnic nerve*. This nerve receives most of the fibres forming the white rami from the lower seven dorsal and upper two or three lumbar roots, the latter fibres often taking a separate course as the lesser splanchnics. The fibres can be seen to pass through the sympathetic chain of the thorax without interruption, and for the most part have their cell station in the large ganglia, especially the semilunar ganglia, of the solar plexus, whence a thick meshwork of non-medullated fibres is distributed along all the vessels of the abdominal viscera. The area of the vessels innervated by this nerve is so large that section of this nerve on each side causes a considerable fall in the general blood pressure. This fall is more marked in animals such as the rabbit and other herbivora, in which the alimentary canal is proportionately very much developed and has a correspondingly large blood supply.

In all cases, the sympathetic supply forms a fine plexus of non-medullated fibres in the muscular coats of the arteries.

VASODILATOR NERVES.—Since the arteries are usually in a constant condition of moderate contraction, a dilatation might be brought about by a relaxation of this tone by an inhibition of the normal constrictor impulses proceeding to the vessels from the vasomotor centre. We find, however, in many parts of the body, evidence of the existence of a nerve supply to blood vessels antagonistic in its function to the vasoconstrictors. Thus, if the *chorda tympani* nerve going to the submaxillary gland be cut, no change is evident in the blood vessels of the gland. But if its peripheral end be stimulated, there is instantly free secretion of saliva from the gland, and all the blood vessels are largely dilated. In consequence of this dilatation, the blood rushes through the capillaries so quickly that it has no time to lose much of its oxygen; the blood flowing from the vein is therefore bright arterial in colour, and is increased to six or eight times the previous amount. If atropine be injected into the animal, the action of the *chorda tympani* on the blood vessels is unaffected, although the secretion on stimulation is abolished.

The chorda tympani is therefore said to contain vasodilator fibres for the vessels of the submaxillary gland. Other examples of vasodilator (or dilator) nerves are the *small petrosal* nerve to the parotid gland, the *lingual* nerve to the blood vessels of the tongue, and the *nervi erigentes* or *pelvic visceral* nerves to those of the penis.

The course of these typical dilator nerves differs widely from that of the constrictors. Whereas the latter leave the central nervous system over a limited area of the cord, the vasodilators take their origin together with any of the cerebro-spinal nerves. Thus, the chorda tympani fibres, and probably those contained in the petrosal nerve, arise from the *nervus intermedius* between the seventh and eighth cranial nerves. The *nervi erigentes* leave the lower end of the cord by the anterior roots of the second and third sacral nerves. All of them, like the vasoconstrictors, and probably all visceral nerve fibres, are interrupted by ganglion cells before reaching their destination. These cells, however, lie not in the lateral chain of the sympathetic, with which the nerves have no connection at all, but peripherally, and are generally embedded in the organs to which the nerves are distributed. Thus the chorda tympani fibres to the submaxillary glands are interrupted by cells embedded in the gland itself. The *nervi erigentes* pass

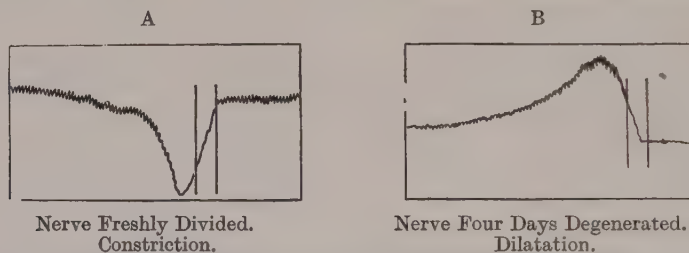


FIG. 440. Plethysmographic Tracing of Hind Limbs, showing effect of Stimulating the Sciatic Nerve on the Volume of the Limb, A, immediately after section of the nerve; B, four days after section. The nerve was stimulated between the two vertical lines. Curves to be read from right to left. (BOWDITCH and WARREN.)

to ganglion cells in the hypogastric plexus lying on the neck of the bladder.

Whether any large numbers of the fibres making up the sympathetic system of nerves are vasodilator in function is still uncertain. In the dog, dilatation of the vessels of the soft palate and gums can be produced by stimulation of the cervical sympathetic of the same side, or of the stellate ganglion, or its *rami communicantes*. The effect has not yet been observed in any other animals. It is probable that the splanchnic nerves convey vasodilator fibres to the vessels of the abdomen, since stimulation of these nerves may cause a fall of blood pressure, provided that the constrictor fibres, which predominate, have been paralysed by the previous administration of large doses of ergotoxine.

The presence of vasodilator fibres in the nerves going to the limbs has been the subject of much debate. Since these nerves also contain constrictor fibres, the effect of the constriction overpowers any effects due to simultaneous stimulation of possible dilator fibres. Moreover, the dilators apparently do not conduct any tonic influences to the blood vessels, so that the only effect of section of a mixed nerve is that due to the removal of the tonic constrictor influences, and the vessels in the area of distribution of the nerves are therefore dilated.

Various methods have been employed to show the presence of dilator fibres in such a mixed nerve trunk. Of these, the two chief are those depending on the unequal time taken for the two sets of fibres to degenerate, and

on the varying excitability of the two sets of fibres to different kinds of stimulation. Thus, if the sciatic nerve be cut, a primary dilatation of the vessels of the leg and foot is produced, which, however, passes off after two or three days. If, now, the peripheral end of the divided nerve be stimulated, dilatation of the vessels is brought about (Fig. 440). Apparently, the constrictor fibres degenerate before the dilator fibres, so that, at a certain period after the nerve section, only the latter respond to stimulation. On the other hand, it is often possible, in the freshly cut nerve, to obtain dilatation by stimulating its peripheral end with induction shocks repeated at slow intervals—one to four per second. The effects of different rates of stimulation on the limb nerves of the cat are shown in Fig. 441.

When we endeavour to trace these limb dilator fibres back to the cord, we find no trace of their passage through the sympathetic system. It was shown by Stricker and Morat that dilatation of the vessels of the hind limb could be produced by stimulating the posterior roots of the nerves going to the limb, *i.e.* far below the point of origin from the cord of the constrictor fibres to the same part of the body.

This was confirmed by Bayliss for all manner of stimuli. Stimulation of the posterior roots, either before or after they have passed through their ganglia, causes dilatation of

the vessels in the area of supply of the roots, whatever be the nature of the stimulus employed, whether electrical, chemical, or mechanical (Fig. 442). This effect is not destroyed by previous section of the posterior roots on the proximal side of the ganglia, showing that the fibres by means of which the dilatation is produced have the same origin and course as the ordinary sensory nerves to the limbs. Since the vasodilator impulses pass along these nerves in a direction opposite to that taken by the normal sensory impulses, Bayliss has designated them as *antidromic* impulses. So far, this phenomenon of a nerve fibre functioning (not merely conducting) in both directions is almost without analogy in our knowledge of the other nerve functions of the body. There is no doubt, however, that similar antidromic impulses are involved in the production of the so-called trophic changes, such as localised erythema or the formation of vesicles (as in *herpes zoster*), which may occur in the course of distribution of a sensory nerve, and is always found to be associated with changes, inflammatory or otherwise, in the corresponding posterior root ganglion. Moreover, evidence has been brought forward that

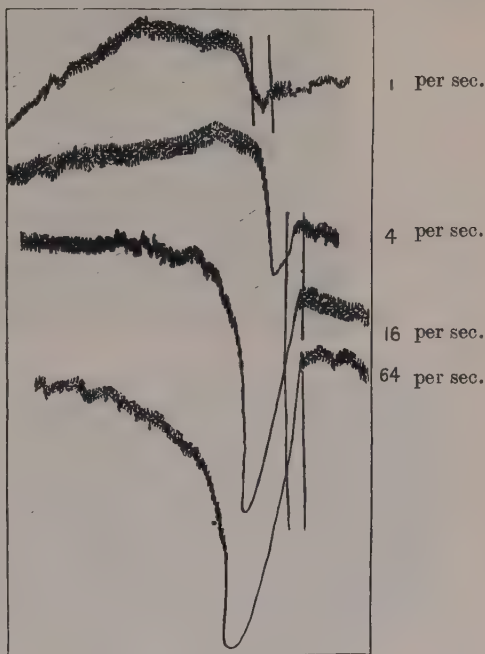


FIG. 441. Effect on the Volume of the Hind Limbs of the Cat of Stimulating the Sciatic Nerve with Induction Shocks at Different Rates.

It will be noticed that with one shock per second there is hardly any constriction, but considerable dilatation, whereas with 64 shocks per second the only effect produced is vasoconstriction. Curves to be read from right to left. (BOWDITCH and WARREN.)

these fibres may take part in ordinary vascular reflexes of the body, that, in fact, they are normally traversed by impulses in either direction.

Some observations by Hans Meyer and Bruce tend to indicate that in

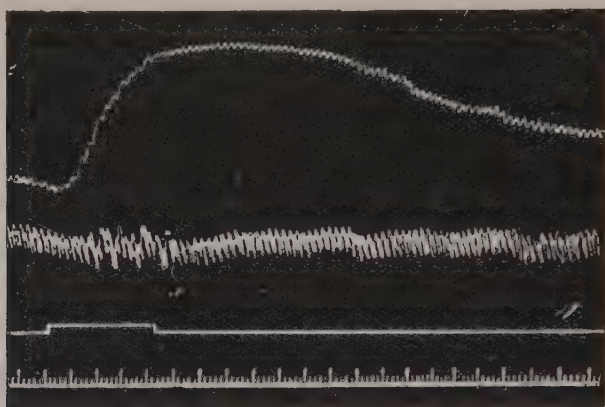


FIG. 442. Effect of Excitation of Peripheral end of the Seventh Lumbar Posterior Root in the Dog. (BAYLISS.)

Uppermost curve, volume of left hind limb; next below, arterial blood pressure; the third line marks the period of stimulation; bottom line, time-marking in seconds.

the antidromic vasodilatation, as well as in the reddening and inflammatory changes of the skin ensuing on local excitation, we are dealing with *axon reflexes*, perhaps the only remains of the local reflexes of a primitive

sup. nerve plex.

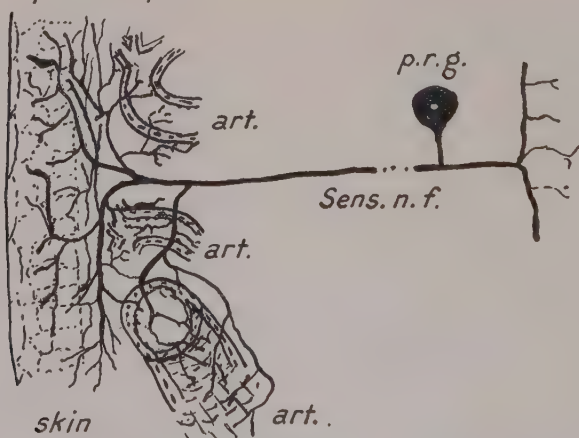


FIG. 443. Diagram to illustrate the Production of Vasodilatation in the Area of Distribution of a Sensory Nerve.

p.r.g. Posterior root ganglion. *Sens. n. f.* Sensory nerve fibre, branching to supply dilator fibres to the skin arteries, and sensory fibres to the skin.

peripheral subcutaneous nervous system. If croton oil or mustard oil be applied to the skin or to the conjunctiva, redness, swelling, and all the signs of a local inflammation are produced. The course of events is not altered by destruction of the central nervous system, or by section of the sensory nerve roots (posterior spinal root or trigeminus) on the central side of the

ganglion. If, however, they be divided peripherally to the ganglion, and time be allowed for complete degeneration of the nerve fibres to their peripheral terminations, the application of croton or mustard oil, even to the delicate conjunctiva, is without this effect. The same results may be produced if the peripheral terminations of the nerves be paralysed by the subcutaneous injection of local anæsthetics. We must assume that the axons of the peripheral sensory nerves branch, some branches going to the surface, others to the muscle cells of the cutaneous arterioles, as indicated in the diagram (Fig. 443).

VASOMOTOR REFLEXES

The vasomotor centre is constantly in receipt of impulses arriving at it from the vascular system, including both heart and blood vessels, and from various other parts of the body. Hence reflex effects are produced by stimulation of various afferent nerves, and these may be classified, according to the area they affect, as general and local.

The afferent impulses affecting the general blood pressure are distinguished as *pressor* and *depressor*, and these names are sometimes applied

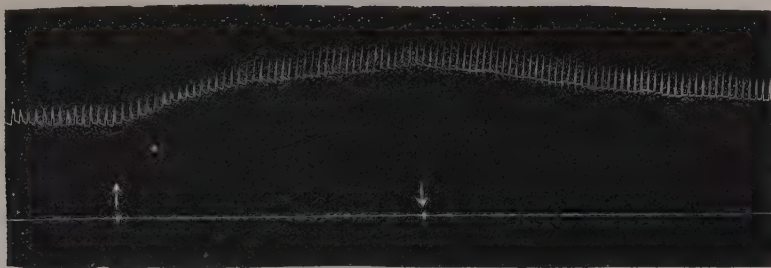


FIG. 444. Blood Pressure Curve from Carotid of Dog. Between the arrows, the central end of a sensory nerve was stimulated. (HÜRTLE'S manometer.)

to the nerves which carry the impulses. A *pressor reflex* is one which induces a rise of general blood pressure by widespread constriction of the blood vessels, usually in the splanchnic area (Fig. 444). Effects of this kind are produced by stimulation of nearly all the sensory nerves of the skin. Practically all impulses, which, if consciousness were present, would be attended with pain, cause also a rise of general blood pressure. A rise of pressure may be produced by the stimulation of such nerves as the fifth, the central end of the splanchnic nerves, or of the nerves distributed to the surface of the body. In the rabbit, when anæsthesia is induced by means of chloral or chloroform, stimulation of sensory nerves may cause a fall of blood pressure.

The chief example of a *depressor* nerve we have already studied in dealing with the reflexes from the heart. The reflex fall of pressure produced by stimulation of the depressor nerve is effected chiefly by dilatation of the splanchnic area (Fig. 445), though, as Bayliss has shown, practically all the vessels of the body partake in the relaxation. The lowering of blood pressure produced by stimulation of this nerve differs from that obtained on stimulating the sensory nerves of the rabbit under chloral, in that its effect lasts as long as the stimulation is continued, whereas in the latter case the effect shows signs of fatigue and disappears before the excitation is shut off.

So far as the general blood pressure is concerned, the most important

impulses arriving at the centre are those from the vascular system itself, especially from the heart, and those from the higher parts of the brain. Whatever the condition of the heart, the brain always demands a high arterial pressure. A failing heart therefore indirectly evokes constriction of the blood vessels, a fact which may lead to a vicious circle in cases where the heart is unable to perform its normal functions and to empty itself against the resistance of the blood vessels.

Under normal circumstances, every part of the body receives just enough blood for its metabolic requirements. Hence, activity must be associated with an increased flow of blood through the part. Two mechanisms are involved in the production of this adaptation. In the first place, there is reflex dilatation of blood vessels in the part concerned, and in the second place, constriction of the blood vessels in the rest of the body, so that a normal or raised blood pressure is available for driving an increased supply of blood through the dilated vessels of the part. Thus, if both hind limbs of an animal be placed in a plethysmograph, it will be seen that stimulation of the central

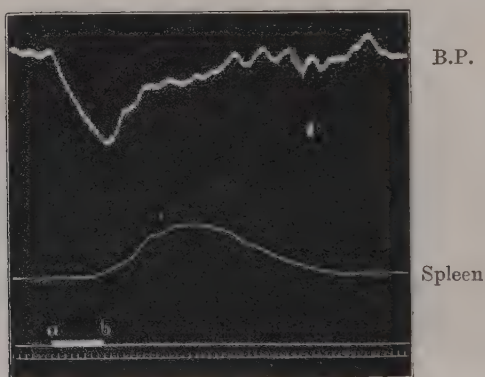


FIG. 445. Simultaneous Tracing of Arterial Blood Pressure and Splenic Volume from a Rabbit, showing the marked swelling of the spleen associated with fall of general blood pressure, on stimulation of the central end of the depressor nerve. The nerve was excited between *a* and *b*. (BAYLISS.)

end of the anterior crural or peroneal nerve in the left leg causes dilatation of this leg and constriction of the leg of the other side. At rest, the organs of the chest and abdomen contain more than half of the total quantity of blood in the body, so that very little change in the capacity of these organs suffices to furnish the extra supply of blood needed by any part during a state of increased activity. In the control of the blood supply to the tissues, the constriction and relaxation of the capillaries probably play a large and special part.

THE CHEMICAL REGULATION OF THE ARTERIOLES

Another factor, which is possibly involved in the production of the increased blood flow through active organs, is a chemical stimulation of the vessels themselves, by means of substances (metabolites) produced as a result of the chemical changes accompanying activity. These substances are continually being produced by the resting tissues, and when the blood supply is stopped for a time, they accumulate. If the blood is readmitted to the tissue, its vessels widely dilate—a condition called *reactive hyperæmia*.

This is illustrated by Fig. 446, in which it is seen that temporary occlusion of the arteries to the hind limbs is followed, after brief constriction, by a large dilatation. The great increase in the flow through the muscles, which accompanies muscular exercise, is probably brought about largely by similar means. It has been shown that the passage of blood containing lactic acid or carbon dioxide (both results of muscular metabolism) causes a marked dilatation of the blood vessels of a limb, but it is certain that the dilatation which occurs in activity is greater than could be accounted for by the presence of these substances, and the actual nature of the substance responsible

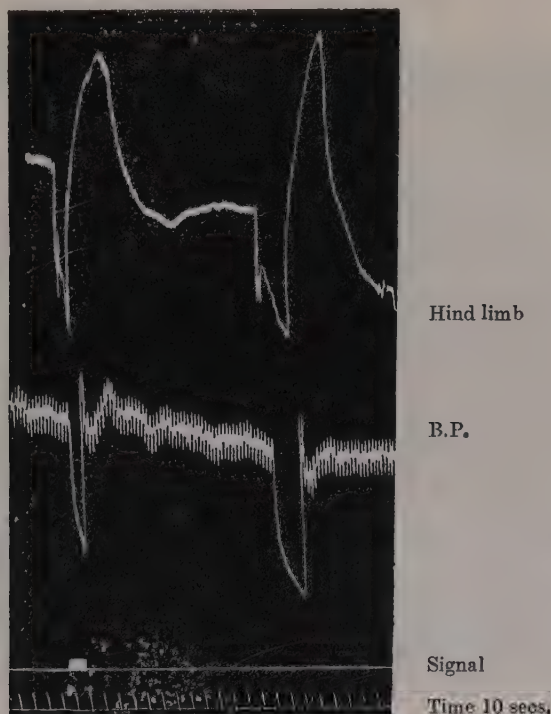


FIG. 446. Effect of Temporary Compression of the Abdominal Aorta on the Volume of the Denervated Hind Limb.

Two compressions, the second not marked by the signal. Blood pressure taken in the femoral artery of one hind limb, the other hind limb being in the plethysmograph. (BAYLISS.)

is open to question. There are, however, indications that it may be acetyl choline, or some closely related substance, which is known powerfully to relax the arterioles.

ACTION OF ADRENALINE. This substance, produced by the suprarenal glands, has a marked influence on the calibre of the blood vessels. If 1 c.c. of a 1 in 10,000 solution of this substance be injected into the jugular vein, there is at once a universal constriction of the arterioles, with the exception of those of the brain. If the vagi are cut, we obtain a simultaneous augmentor action of this drug on the heart, and constrictor effect on the blood vessels, so that the arterial pressure rises to an enormous extent, up to 300 mm. Hg or more. The same result occurs after section of the vaso-motor nerves, or after destruction of the brain and spinal cord, so that there

is no doubt that adrenaline acts directly on the blood-vessel wall. The action of this drug, as a whole, is therefore largely to augment the energy of the circulation. The arterial pressure rises, and the blood will therefore be travelling at a much greater pace through any part of the body where the vessels are maintained in a dilated condition, *e.g.* in an active muscle, or where there are no vasomotor nerves, as in the vessels of the brain. It is therefore not surprising that we have evidence of the secretion of adrenaline in increased quantities into the blood during any condition of stress. When the splanchnic nerve is stimulated, there is an increased production of adrenaline, and the rise of pressure produced shows a stepped curve, the first rise being due to the direct action of the vasomotor nerves on the blood vessels,

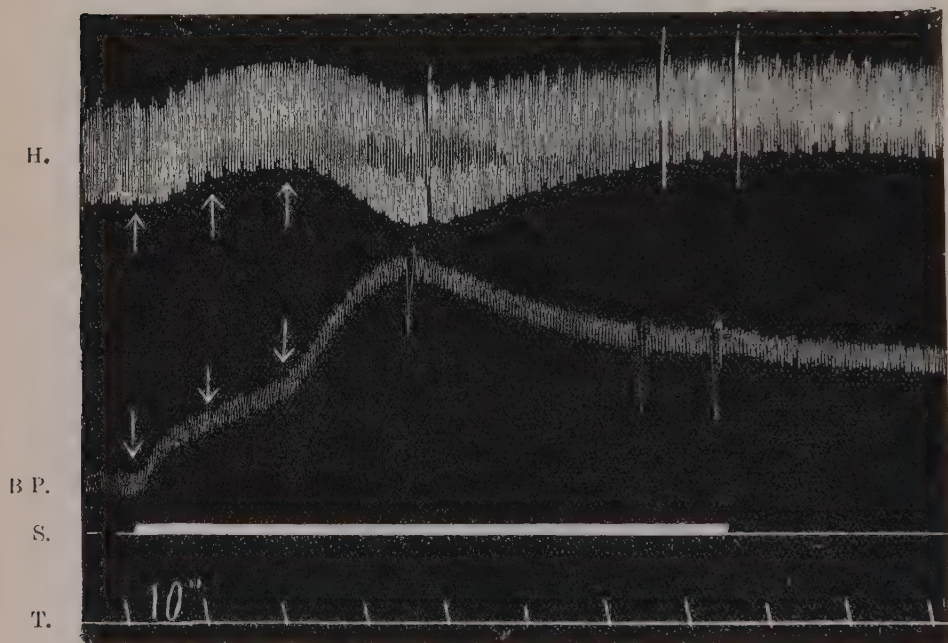


FIG. 447. Curve showing the effect of a Splanchnic Stimulation on the Arterial Blood Pressure and on the Output and Volume of the Ventricles.

Systole causes a downward movement of the lever.

H. Heart volume.

B.P. Arterial blood pressure.

S. Signal showing duration of stimulation of splanchnic nerve.

T. Time-marker, 10 secs.

the second being brought about by the stimulation of the suprarenals and the discharge of adrenaline into the general circulation. Simultaneously with this second rise of blood pressure, we notice in the curve given in Fig. 447 a diminished volume of the heart, signifying a more effective contraction.

This diminished volume of the heart is often associated with a marked quickening of the heart rate, both effects being due to the action of adrenaline on the heart. Similarly in Fig. 448 is shown the effect of brief stimulation of the splanchnic nerve on the blood pressure and on the volume of the limb of the cat. It will be noticed that the volume of the hind limb increases passively with the rise of pressure, and then diminishes much below its previous amount. This diminution is due to the discharge of adrenaline into the

blood stream as the result of stimulation of the splanchnic nerve, and is absent if the suprarenals have been previously destroyed. During asphyxia, the rise of arterial pressure is largely brought about through the intermediation of the splanchnic nerves, and is therefore also associated with the discharge of adrenaline.

THE REGULATION OF THE BLOOD FLOW THROUGH THE CAPILLARIES

Up to the present, we have emphasised only two factors as regulating the blood flow through the peripheral parts of the body, viz. the general blood pressure, and the state of contraction of the arterioles supplying those parts. We cannot, however, regard the minute vessels called capillaries as merely inert channels, the calibre of which depends only on the extent to

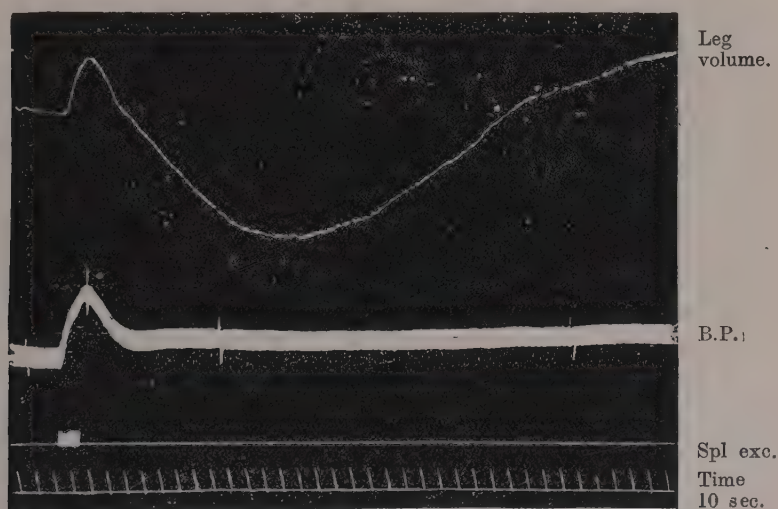


FIG. 448. Effect of Excitation of Splanchnic Nerves on the Blood Pressure and on the Volume of the Denervated Hind Limb of the Cat. (BAYLISS.)

which they are distended by the pressure of blood within them. There is no doubt that both the calibre of, and the resistance to the flow of blood through, the capillaries are determined to a great extent also by the contractility of their own walls. The independent contractility of the minute vessels is well illustrated in the human skin, the colour of which is determined chiefly by the number and size of its minute vessels ('capillaries').

If a blunt point is drawn over the skin, a mark, or *tache*, is left behind. On gentle stroking or on applying pressure with the finger the *tache* is white, and appears in fifteen to twenty seconds, being preceded by transient flushing. When the point is drawn over the skin with a firmer pressure, there is first a light flush (capillary dilatation), followed in fifteen seconds or so by (a) a much deeper flush along the actual track of the instrument (wide dilatation of capillaries and other vessels), and (b) at either side of the red *tache* so produced there appears a white *tache* (capillary constriction). These fade in from three to eight minutes. Microscopic inspection shows that the capillaries and venules in the pale area, though constricted, are in connection with vessels filled with blood, and the emptiness of these vessels can only be due to

the fact that they have actively contracted against the pressure of blood with which they are supplied.

An experiment by Lewis, called the occlusion test, conclusively demonstrates capillary contractility. A Riva-Rocci armlet is placed in position and *rapidly* inflated to a pressure greater than the arterial pressure, *e.g.* 200 mm. Hg. The circulation in the arm is thus suddenly stopped, and the pressure in arteries, capillaries, and veins then becomes equal; as the inflation was rapid, this pressure, though higher than the usual capillary pressure, is not very great. On now applying the skin reaction test, the white *tache* will be found to develop in the usual manner. Now, since the colour of the skin is due to blood contained in the minute vessels, it is evident that in such a limb, with occluded vessels, a contraction of arterioles could not deprive the capillaries of their contained blood, as might be objected if the circulation were proceeding.

Lewis has shown that the red reaction consists of two distinct reactions—a localised one, due to relaxation of *all* the skin vessels, and a spreading flare, due to an axon-reflex, which causes relaxation of the strong arterioles, often for considerable distances, when powerful stimuli have been used.

In a certain number of subjects, the skin after the *tache* tests shows some urticaria, while in others a definite wheal results, owing to the production of local oedema—a condition called *dermatographism*. The *triple response*, local vasodilatation, spreading flare and local oedema, may be obtained by stimulation of the skin by mechanical means, heat, cold, electricity and by various irritant substances, especially histamine.

The dilator effect of metabolites on the arterioles, which we have already studied, seems to be shared by the capillaries. In such a case, it is difficult to dissociate the effects of arterial dilatation from those of capillary dilatation. Acetyl choline, or substances akin to it, chiefly relaxes the arterioles. At least one chemical substance is known, however, which has diametrically opposite effects on the two sets of vessels, *viz.* histamine. This substance has been shown by Dale to have a constrictor effect on the arterioles, and a dilator effect on the capillaries. It, moreover, so increases the permeability of the capillary walls, that fluid rapidly passes out from the blood stream into the tissues. It has been suggested that the production of histamine, or of other substances with a similar action, plays an important part in giving rise to the symptoms of surgical shock. In this condition, which is found notably after widespread laceration, especially of the muscles, and consequent destruction of the tissues, there is a continually increasing depression of the blood pressure, accompanied by an ever lessening volume of blood in circulation. Since this lowering of blood pressure does not depend on any direct action on the heart, nor on vasomotor paralysis, it has been concluded that the prime factor at work is a general dilatation of the capillaries, leading to stagnation of the blood in these vessels, and an increased exudation into the tissues, thus causing a constant leak of blood fluid from the general circulation.

The evidence that these changes are due to the liberation of histamine, or some closely-allied substance, is mainly circumstantial, but very suggestive. There is, first, the fact that histamine can, on injection into the circulation, cause effects closely resembling those seen when surgical shock intervenes as a consequence of extensive tissue damage; or, when injected into the tissues, cause local changes essentially identical with those produced by local injury.

Secondly, there is the fact that histamine (and also choline esters), can be extracted from fresh tissues, particularly the lungs, in which, apparently,

it is either present as such during life, or is produced at the moment of cellular death. The depressor substances present in nearly all tissue extracts have been shown by Dale and Dudley to contain both histamine and esters of choline. Histamine dilates the capillary vessels and choline esters chiefly relax the arterioles, so that either substance produces a fall of blood pressure.

The capillaries are abundantly supplied with nerve fibres, and it has been claimed that capillary constriction has been observed under the microscope on stimulation of the sympathetic nerve supply. Certain facts also point to a connection between nerve lesions and the calibre of the capillaries supplied by the nerves. Thus, if in the cat the sciatic nerve be cut on the right side, for the next few hours the pad of the foot on that side is flushed and warmer than the left foot. The next day the flush has disappeared, in fact the pad of the right foot may be paler than that of the left foot. The right foot is, however, still a degree or two warmer than the left. This condition may be explained on the assumption that the immediate effect of cutting the sciatic nerve is to cause dilatation both of the arterioles and of the capillaries. The capillary dilatation passes off, so that on the day after the section, although the arterioles are still dilated and there is a more rapid flow of blood through the pad and a correspondingly higher temperature than on the sound side, the capillaries are contracted, so that the pad contains less blood and is paler than on the opposite side. These observations suggest the question whether the whole of the antidromic effects, observed by Bayliss to follow stimulation of sensory nerves, may not really be confined to, or have their chief seat in, the capillaries. It is indeed certain that the closely allied phenomena of herpes zoster, and the erythematous eruptions along the course of a nerve, which have their origin in morbid conditions of the nerve or of the posterior root ganglion, are due to changes in the capillaries, or in the tissues immediately around them.

CHAPTER XXXV

THE PULMONARY AND CEREBRAL CIRCULATIONS

IN the lungs there is an extensive system of wide arterioles and capillaries, presenting very little resistance to the flow of blood. The pressure in the pulmonary artery probably does not exceed 15 to 20 mm. Hg, *i.e.* about one-sixth of the mean aortic pressure.

The capillaries of the lungs may vary passively in size, according to the condition under which they may be placed. Thus, whereas at the height of inspiration the blood contained in the lungs is about one-twelfth of the whole blood in the body, this amount is said to be diminished during expiration to between one-fifteenth and one-eighteenth, and by forcible artificial inflation of the lungs may be lessened to one-sixtieth. Such changes may exercise a considerable effect on the systemic blood pressure. On the other hand, the distensibility of the lung capillaries may play an important part in enabling the lungs to act, so to speak, as a reservoir for the left side of the heart. If, in consequence of raised arterial pressure or other factor, there is a temporary excess of output on the right side that cannot be dealt with at once by the left heart, the excess is taken up for a time in the lung capillaries.

Vasomotor fibres to the lung vessels have been described as running in the anterior roots of the third, fourth, and fifth dorsal nerves. Their action is, however, of little importance. The fact that injection of adrenaline causes some vasoconstriction in the lungs, points to the presence of a vasomotor sympathetic supply to those organs. But under normal conditions, changes in the calibre of the lung arterioles play very little part in determining the pressure in the pulmonary artery, or the resistance to the expulsion of the contents of the right ventricle. On the other hand, considerable changes in the pulmonary pressure are induced by altering the inflow into the right heart, and thereby the velocity with which the blood must be propelled through the pulmonary vessels. Thus it has long been known that a rise in the aortic pressure, while the venous inflow into the heart is kept constant, is accompanied by a corresponding rise in the pulmonary artery pressure. This has been often ascribed to 'back pressure,' *i.e.* to a relative failure of the left heart to deal with the blood flowing into it. Anrep has shown, however, that in the heart-lung preparation, the whole pulmonary rise under these conditions is due to the increased flow through the coronary arteries induced by the rise of aortic pressure. It is probable that similar conditions largely contribute to the parallelism between pulmonary and systemic arterial pressures in the intact animal, and that in normal hearts the left auricle is competent to keep the pulmonary veins adequately, but never excessively, drained. Only when the left ventricle is greatly dilated and the mitral valve incompetent, are there likely to be pronounced back pressure effects.

EFFECT OF RESPIRATION ON SYSTEMIC BLOOD PRESSURE.

If we examine a tracing of the arterial blood pressure, we notice that

with each inspiration the blood pressure rises, and with each expiration it falls. The synchronism of the rise and fall with the respiratory movements is not exact, since the rise continues for a short time after the beginning of expiration, and the fall continues right into the beginning of the next inspiration, so that the highest point of the curve occurs at the beginning of expiration and the lowest point at the beginning of inspiration. During the fall which accompanies expiration, the heart beats often become less frequent. On dividing both vagi, this difference in the pulse rate during inspiration and expiration disappears, but the main features of the blood pressure curve remain the same; so that we must look for some mechanical explanation of the respiratory undulations.

We have already seen that, under normal conditions, the lungs are in a state of stretch, and that in consequence of this condition they are constantly tending to collapse, and are therefore exerting a pull on the chest wall. As soon as we admit air into the pleural cavity, the lungs collapse. As the chest expands in inspiration it drags the lungs still more open, so that their pull on the chest wall becomes greater, and hence the negative pressure in the pleura is much increased during forcible inspiration. It must be remembered that the heart, great veins and arteries in the thorax are separated from the pleural cavity only by a thin yielding membrane, so that they are practically exposed to any pressure, positive or negative, which may exist in the pleural cavity, whereas outside the thorax all the vessels are exposed to a positive pressure.

Blood, like any other fluid, will always flow from a point of higher to a point of lower pressure. Hence when the thorax enlarges during inspiration, there must be an aspiration of blood into it from peripheral parts. This aspiratory force will not influence arteries and veins alike. The arteries, having thick, comparatively non-distensible walls, will be very little affected by the increase of negative pressure in the thoracic cavity, whereas the thin-walled distensible veins will be largely influenced. The total result, then, of the increasing negative pressure in the pleural cavities, is to increase the flow of blood from the veins into the heart, without affecting to any appreciable degree the outflow of blood from the heart into the arteries. The more pronounced the fall of pressure in the thorax, the greater will be the amount of blood sucked into the heart from the veins. *During* inspiration, therefore, the inflow into the right heart will be more rapid than during expiration, and this factor in itself will tend to raise the arterial blood pressure. The inspiratory descent of the diaphragm will, moreover, tend to increase the inflow into the heart by raising the positive pressure in the abdomen, so that the blood is pressed out of the abdominal veins, and sucked into the heart and the thoracic veins. During expiration, all these effects are reversed.

Some authors have ascribed considerable importance to changes in the circulation through the lungs under the influence of the respiratory movements. Although extreme expansion of the lungs increases the resistance to the flow through their vessels, presumably by lengthening and narrowing the latter, moderate respiratory movements have very little effect in either direction. There are, however, probably some effects of altered capacity of the distensible thoracic vessels, both inside and outside the lungs. When the thorax expands, the immediate effect of the pull on the vessels that have thin walls is to fill them up with blood, and this extra blood being diverted from its onward movement leads at first to a reduced flow into the left ventricle. Hence, at the onset of inspiration, the systemic blood pressure falls even further than during expiration. For the converse reason that the expanded vessels partly empty at expiration, and add the blood so expelled to the pul-

monary current, the systemic pressure at the commencement of expiration continues still further the rise established during inspiration. Lewis regards the pericardial pressure, *i.e.* the direct influence of the thoracic movements on the heart, as playing a much more important part than changes in the pulmonary circulation in the production of the respiratory undulations in the blood pressure. He shows, moreover, that in man, the effect of respiration on arterial blood pressure may vary according to the type of respiratory movement, a deep intercostal inspiration (not prolonged) causing a pure fall, while a deep diaphragmatic inspiration gives a pure rise of blood pressure. In expiration the reverse effects hold. He concludes that, in man, it is not possible to make any *general* statement as to the nature of the blood pressure response to a particular respiratory act.

THE CEREBRAL CIRCULATION

The grey matter of the brain is very richly supplied with blood vessels. Any interference with the blood flow through the brain rapidly checks the functions of the central nervous system in consequence of deprivation of oxygen. Although so susceptible to slight deprivation of oxygen, it does not seem that the brain tissues have a very rapid gaseous metabolism; that is, they need oxygen supply at high tension, but do not deprive the blood of any very large amount of the oxygen which it contains. Nor does it seem probable that the brain requires a large supply of food material.

In all higher animals, the brain is enclosed in a rigid case formed by the bony cranium. In the child, before the cranial vault is fully ossified, part of this vault consists of membrane, known as the anterior fontanelle. It is easy to see that the fontanelle pulsates with each heart beat, as well as with rise of venous pressure, such as that produced during strong expiratory efforts. When ossification is complete, such alterations in the volume of the cranial contents are impossible. And yet the pressure in the arteries within the cranium must be still pulsatile, the rise of pressure at each heart beat must make the arteries expand, but room for this expansion has to be found by contraction of some other part of the cranial contents. We find that each arterial beat is associated with a corresponding expulsion of some of the contents of the veins, and a compression of these vessels. If, for instance, a canula be introduced through the occipital bone into the torcular Herophili, the venous blood is seen to pulsate and to be pressed out with each beat of the heart. If there is a rise of arterial pressure, although the arteries may expand somewhat at the expense of the veins, there can be no dilatation of the whole organ. The only effect of the rise of pressure will be to cause an increased pressure slope in the cranial vascular system, and therefore augmented velocity of flow through the system. A prolonged rise of pressure may cause a certain amount of dilatation of the vessels, but only at the expense of the cerebrospinal fluid. Since this is small in amount, any expansion of the brain due to vascular causes must be very limited.

BRAIN PRESSURE. If, by means of a trephine, an opening be made into the cranial vault, the brain bulges into the opening. By screwing a tube covered with a membrane into the trephine opening, we can find the pressure necessary to force the brain back to its previous position. This is known as the intracranial pressure; it is, as might be expected, approximately equal to the cerebrospinal pressure and to the pressure in the venous sinuses, and is closely dependent on the latter. Forced expiratory efforts, such as may occur in the convulsions of strychnine poisoning, may raise the pressure from 30 to 50 mm. Hg. In the vertical position, in man, the pressure may be slightly

negative, in consequence of the tendency of the venous blood to run downwards towards the heart.

REGULATION OF THE BLOOD SUPPLY TO THE BRAIN. No satisfactory evidence has been brought forward of the existence of vasomotor nerves controlling the calibre of the cerebral blood vessels. Nor, indeed, are such nerves necessary. The brain, as the master tissue of the body, and acting through the medullary centres, controls the circulation through all other parts of the body. It is therefore able to regulate the blood supply through its arteries by allowing less or more blood to pass through other parts of the body. For the exercise of its normal functions, it requires a certain blood supply, which again will depend simply on the pressure in the carotid arteries and circle of Willis. If this pressure fails, the functions of the brain are affected and loss of consciousness rapidly ensues. This is what occurs when a person, who is weak from long illness, faints on suddenly getting up from bed. In the normal individual, the change in the circulation with alteration of bodily position, which would be produced by the action of gravity, is at once counteracted through the vasomotor system. The splanchnic area is contracted or dilated according to the necessities of the case, but the pressure in the carotid, and the circulation of the brain remain unaltered. Even when the heart, in consequence of disease, is scarcely able to carry on the circulation, the arterial pressure undergoes little or no alteration. Any other tissue of the body, even the heart itself, may suffer, but the brain at all costs must receive its proper supply of blood.

CHAPTER XXXVI

THE REGULATION OF THE CIRCULATION

THE CIRCULATORY CHANGES DURING MUSCULAR EXERCISE

In the preceding chapters we have analysed somewhat artificially the factors which are normally involved simultaneously in the adaptation of the circulation to the necessities of the body. Our view of the working of the circulation as a whole is imperfect until we can effect a synthesis of these isolated mechanisms, and trace out the chain of events concerned in the intimate co-operation of all parts of the circulation with all other systems and organs of the body. For this purpose, we may take as an example the adaptations which are involved in muscular exercise. For the analysis of the different events in the circulation, we have hitherto had large recourse to animal experiments; but with the facts thus gained at our disposal, we can proceed to investigate the subject on man himself, with the added advantages of his voluntary co-operation and of the absence of abnormal conditions such as anæsthetics, &c.

On initiating such experiments in man we meet at once with a new fact—viz. that under normal circumstances the reflex and automatic adaptation of the heart and vessels is forestalled and reinforced by the active intervention of impulses proceeding from the brain. Thus, the willed effort, or the emotion of fear or anger which normally initiates extensive muscular movements, gives rise at the same time to impulses, starting in the brain, which excite changes in the circulatory and respiratory systems such as anticipate those which will be later excited reflexly or automatically as a result of the exercise. With a man seated on a stationary bicycle the mere question "Are you ready?" evokes increase of muscular tone in the act of attention, increased pulmonary ventilation, and a rise of pulse rate and of blood pressure. And these changes are increased as soon as the word "go" is given and the man starts to pedal, *i.e.* before the increased metabolic changes in the muscles can have had time to affect the medullary centres, or the muscular contractions the vigour of the circulation. The reinforcing impulses from the cortex, which stimulate the medullary centres and put these various mechanisms into action, are effective especially at the beginning of muscular work. In any steady work produced without particular effort or attention, the subsequent adaptations of the different organs of the body are probably chiefly automatic, the central reinforcing impulses being of especial importance when, under emotional stress of any description, the animal has to put forth its maximum effort.

We have seen that the oxygen intake, and the CO_2 output, may undergo a ten or twelve fold augmentation during violent muscular effort carried out for a short time, and a five fold increase is common, and may last for

many hours. A necessary condition of all muscular exercise is that the muscles shall be supplied with oxygen in proportion to their requirements. Since the arterial blood is, under normal conditions, almost saturated with oxygen, such increases in the oxygen usage by the muscles must imply a great increase in the blood supplied to them, though a certain extra amount of oxygen may be gained by a more complete utilisation of the oxygen of the blood as it flows through the working tissues. This increased oxygen traffic involves, in its turn, an increase in the blood flow through the lungs and in the ventilation of the lungs. The circulation through the lungs is identical with the output of the right ventricle. This has been investigated by Krogh and Lindhard and by Means and Newburgh in the healthy man during rest and during exercise. In Fig. 449 are shown results obtained by the two last-

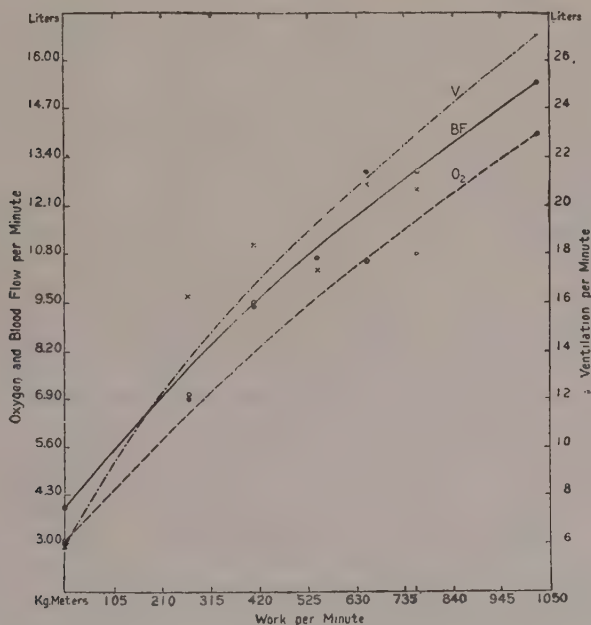
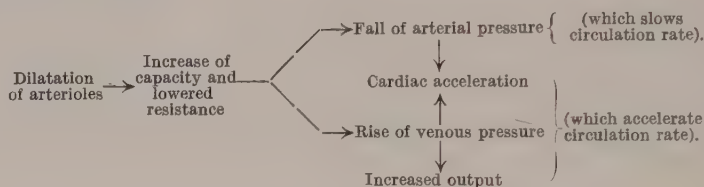


FIG. 449. Chart showing the Effect of Increasing Amounts of Muscular Work on the total Ventilation of the Lungs V , on the Blood Flow, BF , and on the Oxygen Absorption, O_2 . (From MEANS and NEWBURGH.)

named observers. It will be seen that the blood flow through the lungs, *i.e.* the output of the right ventricle per minute, increases in a manner almost absolutely proportional to the consumption of oxygen, and that both increase *pari passu* with the work done per minute. How is this admirable adjustment of the activity of the heart and circulation to the oxygen needs of the muscles effected? The output of the heart depends on the inflow into this organ, so that our problem is to determine the factors which increase the inflow into the heart. At or before the onset of muscular exercise, unless this is quite moderate, there is relaxation of the muscle vessels and contraction of the splanchnic vessels, so that the blood is diverted from the viscera to the muscles and later on also to the skin. Other things being equal, it is evident that, since the blood moves in a circle, any circumstance which favours the passage of blood through the circuit as a whole, will lead to an

acceleration of circulation rate, and this will take the form of a more rapid return of blood to the heart. But, as a matter of fact, there will also be accompanying changes operating in the opposite direction, by which the result is to some extent complicated. Thus, if we imagine a simple circulation, it is clear that extensive dilatation of the arterioles will give rise to the following chain of events :



In consequence of such changes, the alterations of arterial pressure are much smaller than they would otherwise be, since they are to a considerable extent compensated for by the accompanying alterations in the cardiac output. This is further augmented in exercise in a variety of ways. Every muscle, as we have seen, acts as an accessory heart, the muscular contractions emptying the capillaries into the veins, and in the latter driving on the fluid towards the heart in virtue of the valves present in these vessels. The more active the muscles, therefore, the more rapidly the blood which enters them is passed on with force towards the big veins and the heart. The circulation through the big veins of the abdomen and chest is aided by the respiratory movements, which are also augmented in proportion to muscular activity, each inspiration driving the blood out of the big veins in the abdomen and aspirating it into the thorax. The blood flow into the heart is thus increased in proportion to the activity of the muscles. The first effect of muscular exercise will be to increase the filling of the heart and therefore the output at each beat. The increasing tension on the venous side of the heart evokes reflexly a quickening of the heart rhythm, chiefly by inhibition of the vagus tone, possibly also by reflex stimulation of the sympathetic accelerator nerves. Further increase in the inflow into the heart is met by corresponding quickening of the heart rhythm and the output of each ventricle per minute is increased seven to ten times. The part played by increase of output per beat, and by increase of pulse rate respectively, in augmenting the total output of the heart is shown in Fig. 450. In this figure, the first rise in pulse rate from sixty-eight to ninety-eight, and the corresponding increase in output per beat, can be regarded as associated with the initial changes originated by the act of attention and volition. It will be seen that between 270 and 600 kilogrammetres of work per minute the pulse rate remains practically unchanged, while the output per beat increases steadily with the work. After this point, there is very little further increase in the output per beat, which towards the end begins to diminish, while there is a steady increase in the pulse rate.

By this means, the blood is driven through the lungs at a rate corresponding to the increased needs of the muscles for oxygen. The passage of this blood through the muscles is provided for by two mechanisms. In the first place, we have the contraction of the splanchnic vessels, so that the blood pressure is kept up, or raised, and all the available blood can be driven through the working tissues. In the second place, the muscles in their activity produce lactic acid, CO_2 , and other metabolites, which cause dilatation of the arterioles and capillaries in the muscles themselves. During rest, it is probable that the majority of the capillaries are closed ; during activity

these dilate and are filled with blood, so that the capillary bed in the muscles may be increased many times in area, and each element of the muscle is brought into close relation with a dilated capillary, through which is flowing a rapid stream of oxygenated blood. Krogh has shown that the number of blood-containing capillaries in each square millimetre cross-section of the muscle may be increased 40 to 100 times during maximal activity of the muscle. As a result, the oxygen tension in the muscle fibres becomes almost equal to that in the capillaries themselves.

The production of acid products in the muscles also aids dissociation of the oxy-hæmoglobin passing through the capillaries, and therefore sets free oxygen for the use of the muscles. On this account, we find almost invariably that the utilisation of the oxygen taken in from the lungs is more complete during exercise. The oxygen utilisation of the blood as it flows round the circulation is known as the 'co-efficient of utilisation.' Thus if 328 c.c. of oxygen were used per minute and the blood flow were 4.5 litres per minute, $\frac{328}{4.5} = 73$ c.c. oxygen would be utilised per litre of blood. If the oxygen capacity of the blood were 193 c.c. per litre, the co-efficient of utilisation would be $\frac{73}{193} = 38$ per cent. In Fig. 450 the co-efficient of the oxygen utilisation is given by the curve C.

It has been shown by Cannon that every state of excitement, and especially fear and anger, is attended with increased secretion of adrenaline into the blood stream. During violent exercise associated with emotional stress, there will be an excess of adrenaline circulating in the blood, and this will reinforce the activity of the circulation. Thus, it will increase the constriction of the splanchnic area, already excited reflexly and by the central effects of the increased CO_2 or lactic acid in the blood. In the heart, the adrenaline will increase the contractile power and also the rate of beat, while, by its dilator action on the coronary vessels, it will aid the supply of oxygen to the heart muscle. At the same time, as we have seen (p. 646), adrenaline will cause a rapid conversion of the glycogen of the liver into sugar, so that the contracting muscles will be adequately supplied with the food which they can utilise with the greatest ease and readiness. It is doubtful whether these adjuvant effects of adrenaline are to be reckoned with, except in cases of severe emotional stress.

Training. The muscular efficiency of a man is measured by the extent to which he can call upon his body for increased efforts, *i.e.* by his margin of response. Over a moderate period of time, the individual may increase his

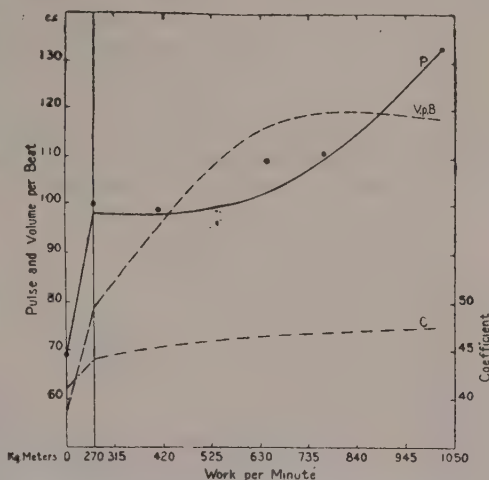


FIG. 450. Chart showing the Effect of Increasing Amounts of Muscular Work on the Pulse Rate, P, shown by dots; on the Heart Output per Beat, VpB, and on the Co-efficient of Oxygen Utilisation in the Blood, C. (From MEANS and NEWBURGH.)

muscular work, his respiratory exchange, and the rate of his circulation six times above that which obtains during rest. In a sudden or short-lasting effort, a much greater amount of energy can be put out, the muscles working to a large extent anaerobically with the production of lactic acid, which undergoes oxidative removal after the cessation of the effort. In this case the individual 'goes into debt' for the necessary oxygen. The performance of a normal individual can be increased by training, the essential features in which are graduated exercise and healthy diet, so that the muscle grows and becomes free from interstitial fat, while the fluid parts of the body and of the blood are diminished so that a larger amount of oxygen

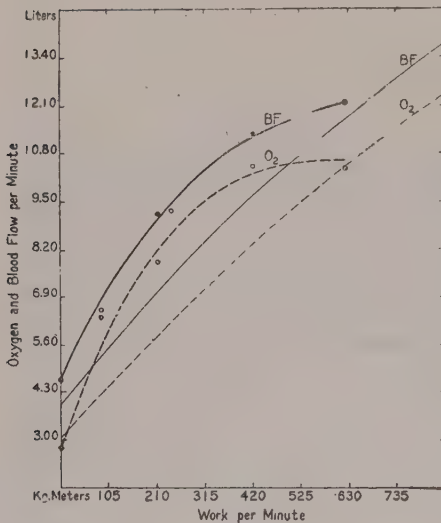


FIG. 451. Chart showing the Effects of Muscular Work on the Blood Flow and Oxygen Consumption in a subject with Aortic Disease, as compared with a normal individual (shown in lighter lines). (From MEANS and NEWBURGH.)

(For oxygen consumption omit the decimal point and read in c.c.s.)

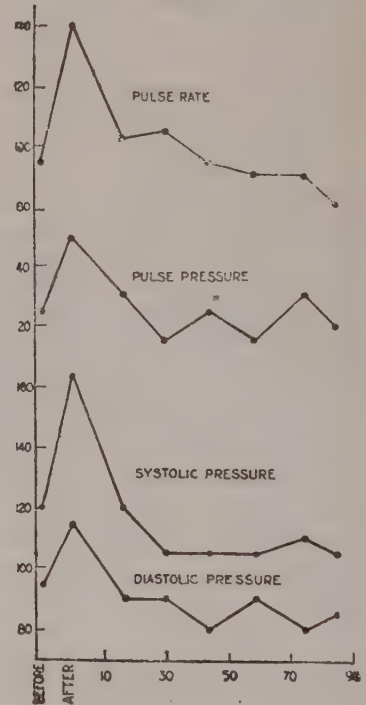


FIG. 452. Curves showing the Influence of Exercise on the Circulation. The exercise was a six-mile run. Ordinates = mm. Hg pressure and rate per minute. (O. S. LOWSLEY.)

can be carried per unit volume of blood. The well-trained individual may have a margin of as much as 1200 per cent. Disease is marked by a diminution of the margin. In Fig. 451 is given diagrammatically the response of the circulation and respiration of a man with heart disease affecting the aortic and mitral valves. This man had no discomfort and was able to do ordinary work without ill effects. On testing him on measured muscular tasks, it will be seen that, although at first he reacts like the normal individual, his margin is diminished, and when doing only 315 kilogrammetres of work per minute, the rise in the oxygen intake and in the heart output fails to keep pace with the increase in the work and also loses the parallelism which is so marked a feature in normal individuals. With increasing disease,

the time would finally come when the margin was reduced to 50 per cent. or 100 per cent., so that even the act of changing from a recumbent to an erect position might be too much for the enfeebled adaptive mechanisms of the body, and the patient would have to keep to his bed. There is thus no definite dividing line between health and disease, the change from one to the other being but a progressive diminution of margin or extent of adaptation.

We have seen that the physiological condition of the heart is measured by the degree of dilatation of its cavities, *i.e.* of the length of its muscle fibres, required in order that in its beat it may set up a contractile stress adequate to expel its contents against the arterial resistance. Thus a degree of filling of the heart, which in a well-trained man may be adequate to excite a contraction sufficient entirely to empty its cavities, in a weaker heart would be inadequate, so that blood would accumulate at each diastole until the stretching of the fibres was sufficient to ensure that the amount entering during diastole was expelled at each systole. The trained man—*i.e.* with a heart in good condition—will therefore have a considerable range over which the output per beat can be increased with increasing inflow, without alteration of rhythm. In the untrained man this margin will be smaller, so that the second mechanism of adaptation, *viz.* quickening of the heart beat, will be sooner brought into action to cope with the increased inflow associated with muscular exercise. Thus, one finds a considerable difference in the effect of exercise on the pulse rate in trained and untrained individuals respectively, and this is especially shown in the promptness of recovery of the pulse when the exercise comes to an end, the effects lasting much longer in the untrained. In all cases exercise not carried to exhaustion tends to be followed by a prolonged diminution both in pulse rate and in blood pressure (*cf.* Fig. 452).

THE INFLUENCE ON THE CIRCULATION OF VARIATIONS IN THE TOTAL QUANTITY OF BLOOD

PLETHORA AND HYDRÆMIC PLETHORA

The effects of increasing the total volume of circulating fluid may be studied by injecting several hundred cubic centimetres of defibrinated blood or normal saline solution into a vein. In the latter case, since the blood is rendered more dilute, the condition is called hydræmic plethora (*Fig.* 453). On the arterial pressure the result of such an injection is not very marked. There is a slight initial increase in the pressure, but the increase is by no means proportional to the amount of fluid injected, showing that the excess fluid is not to any large extent contained in the arterial system. On examining the pressure in the veins, however, we find a very great relative rise of pressure, and on opening the abdomen it is seen that all the veins are distended and that the liver is swollen. The organism prevents the rise on the arterial side by relaxing the whole system of arterioles, so that the distribution of pressures is altered, and the venous approximates more closely to the arterial pressure. This arterial dilatation augments the velocity of the blood: *e.g.* the velocity may be accelerated to six or eight times the normal rate by injecting an amount of salt solution equivalent to 50 per cent. of the total blood.

The high venous pressure causes increased diastolic filling of the ventricles, and therefore augments the strength of the beat. If the vagi are intact, the frequency is also generally raised, in consequence of the greater

distension of the auricles. Thus, the work of the heart is increased in three ways, viz. by

- (1) Rise of arterial pressure.
- (2) Greater frequency of beat.
- (3) Increased output at each beat (Fig. 454).

These series of changes result in the relief of the vascular system. The rise of pressure in the aorta causes a reflex dilatation of all the arterioles of the body, through the depressor fibres of the vagus nerve. At the same time, the increased pressure and blood flow in the vessels of the brain causes a general arterial dilatation by its direct influence on the vasomotor centre. The heightened pressure in the abdominal veins and capillaries causes a great

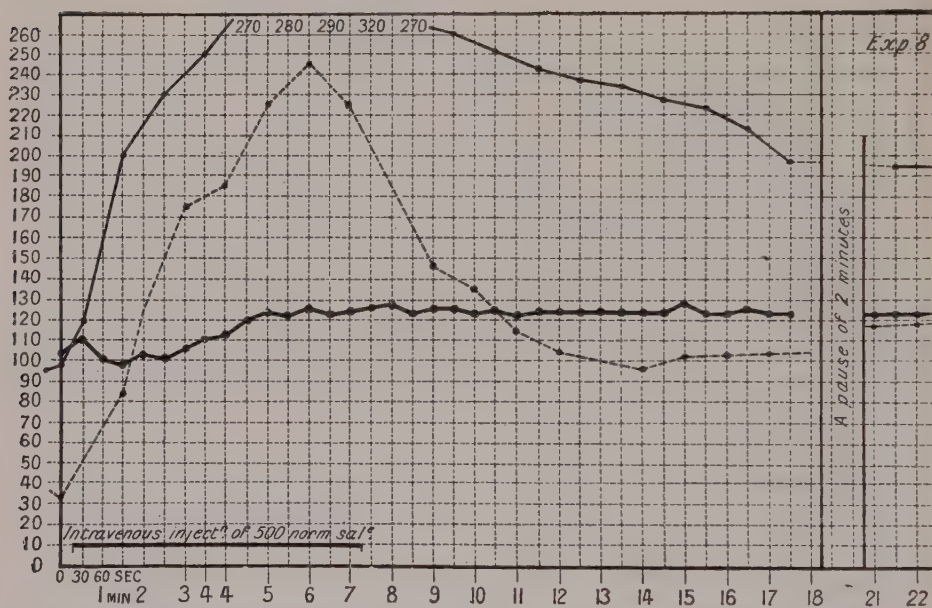


FIG. 453. Effects of Hydræmic Plethora on the Pressures in the Carotid Artery (thick line), Portal Vein (thin line), and Inferior Vena Cava (dotted line). (BAYLISS and STARLING.)

The arterial pressure is in mm. Hg; the venous pressures in mm. H₂O.

leakage of fluid, in the form of lymph, from the capillaries of the intestines and liver, while the increased pressure and velocity of the blood in the glomeruli of the kidney induce a copious secretion of urine, so that within a couple of hours after the injection of salt solution, the volume of the circulating fluid may have returned to normal.

This recovery is effected with greater difficulty if the plethora has been brought about by the injection of blood, or of saline containing 8 per cent. of gum arabic, since these fluids exert a colloidal osmotic pressure, and cannot escape so rapidly from the capillaries, nor be excreted unchanged by the kidneys. Hence it is easy to kill an animal by wearing out its heart, if too large quantities of blood be injected.

In the transfusion of blood it is essential to use blood from the same species of animal, or, in man, that of a person of a compatible blood group (*v. p.* 689); otherwise agglutination, hæmolysis and toxic symptoms follow.

THE EFFECTS OF HÆMORRHAGE. ANÆMIA

Any diminution of the total volume of the blood, as by bleeding, would tend to lower the pressure on both sides of the system. The vasomotor centre, however, reacts to maintain the normal arterial pressure, and so the circulation through the brain, unaltered. This is attained by a general vascular constriction, which diminishes the total capacity of the system and alters the distribution of pressures throughout the system, so keeping the blood as much as possible on the arterial side. Hence, a slight loss of blood has no influence on the arterial blood pressure, but causes a fall of pressure

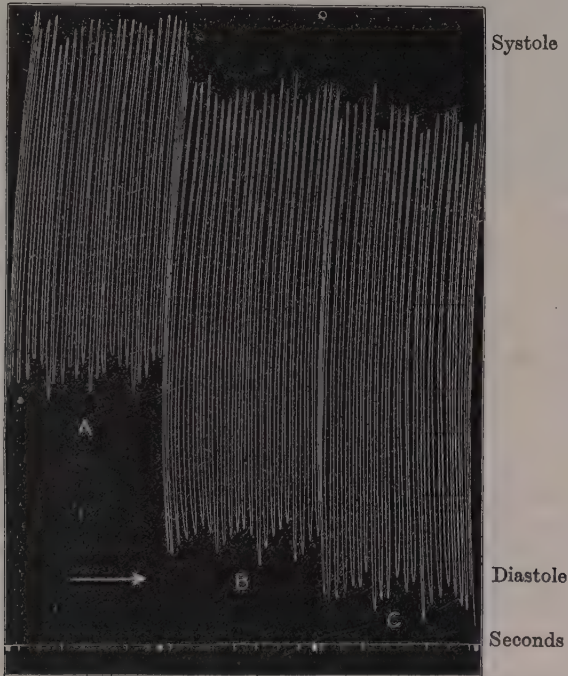


FIG. 454. Cardiometer Tracing from Dog's Heart to show Effect of Increasing the Volume of Circulating Blood (Hydræmic plethora) on the Total Output and the Volume of the Heart. (ROY.)

Between the parts A and B 30 c.c. of warm normal salt solution were injected intravenously, and between B and C 20 c.c. more. It will be noticed that both the systolic and the diastolic volumes are increased, *i.e.* the heart is more distended during diastole, and does not contract to its normal size in systole. The contraction volume, and therefore the output, is very largely increased.

in the veins, blanching of the abdominal organs, and diminished flow of urine. The heart beats more frequently, and so aids in emptying the venous into the arterial system.

The deficiency of circulating fluid caused by bleeding is soon remedied by a transfer of fluid from the tissues to the blood. This transfer is independent of the flow of lymph from the thoracic duct into the blood, and is the direct consequence of the universal fall of capillary pressure which results from the bleeding. The abstraction of fluid from the tissues is responsible for the extreme thirst which is the result of hæmorrhage. The transfer of fluid from tissues to blood is extremely rapid; even during the course of a bleeding, it is found that the later samples of blood are more dilute than those

obtained at the beginning. This mechanism suffices only to make up the supply of circulating fluid. After a bleeding, however, an animal has lost proteins and blood corpuscles, and these constituents of the blood are but slowly restored, the former indirectly from the food, the latter by an increased activity of the blood-forming cells in the red marrow.

Physiological Alterations in the Filling of the Vascular System. The volume of blood in the body is not quite constant, but often undergoes small and rather rapid fluctuations owing to an altered balance of loss and gain of fluid through the capillary walls. Thus, a rise of arterial pressure is accompanied by concentration, and a fall by dilution, of the blood, as if to compensate.

The general capacity of the vascular system is also variable. The most variable part of the system in this respect is that represented by the great veins; these in the human subject can hold 500 c.c. or more when distended, but usually they form baggy reservoirs of very variable content. The capacity of the venous system enters into the question in a very important way, viz. in relation to the portal circulation. The liver receives a very abundant supply of blood, and often about one-third of the blood in the body passes through that organ per minute. Not only is the volume which passes great, but the channels through which it is conducted are wide, so that the amount of blood present in the liver at any moment is considerable. The portal vein, with its rootlets, represents a reservoir intercalated between two resistances, viz. the arterioles of the splanchnic area centrally, and the smaller liver vessels peripherally. This reservoir when distended can hold about a third of the blood in the body. Filling of the portal reservoir can be effected by dilatation of the primary (splanchnic) resistance or by constriction of the secondary (hepatic) resistance, and conversely a partial emptying of the reservoir results from constriction of the primary and/or dilatation of the secondary resistance. Such a partial depletion of the portal venous system is what happens, for instance, in exercise, or when the splanchnic nerve is stimulated; the result is a fall of portal pressure, a rise of caval pressure, and a greatly increased venous return and cardiac output, which is due to a virtual increase in the amount of blood in the circulatory current.

THE SPLEEN

The spleen may be regarded as a further special part of the portal system, which, among other functions acts especially as a reservoir for red cells. The recent work of Barcroft has shown that the size of the spleen varies with the physiological requirements, as such a view would anticipate.

This organ is similar in many respects to a lymphatic gland. It is formed of a framework of connective tissue and unstriated muscular fibres, in the interstices of which is contained the *splenic pulp*. This consists of a fine fibrillar network, on the fibrils of which lie cells belonging to the reticulo-endothelial system. The meshes contain the cells of the splenic pulp, which are fairly large pulp cells, or splenocytes, red cells, and leucocytes. The blood from the splenic pulp is collected into large venous sinuses, also lined by reticulo-endothelial cells, which run along the trabeculæ to the hilum, where they unite to form the splenic vein.

The arteries to the spleen are beset in their course along the trabeculæ with small nodules of lymphoid tissue, which are known as the Malpighian follicles. These contain germinal areas in which, by division, new lymphocytes are produced, and as in other lymphoid tissues, find their way into the blood. The arteries yield a few capillaries which

supply the Malpighian follicles, but for the most part open either directly into the venous sinuses, or else, by way of curious perforated sacs, into the pulp. From the pulp, the blood can pass by numerous spaces into the venous sinuses, and so into the splenic vein.

There are thus alternate paths for the circulation through the spleen ;

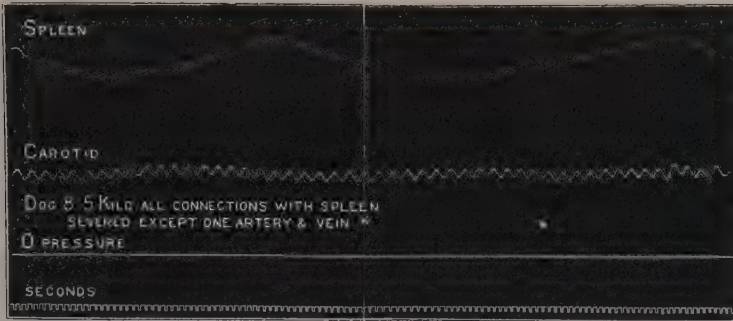


FIG. 455. Plethysmographic Tracing of Spleen (upper curve) from a Dog, showing the Spontaneous Contractions of this Organ. (Reduced from a tracing by SCHAFER.)

that from arteries direct to sinuses is probably free, but it is evident that the blood must meet with considerable resistance in passing through the close meshwork of the splenic pulp. This path of the circulation is, however, assisted by the occurrence of rhythmic contractions of the plain muscle forming the capsule and trabeculae. If the spleen be enclosed in a

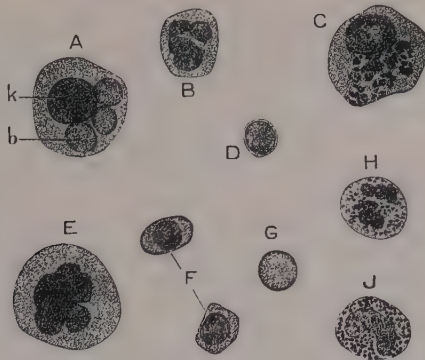


FIG. 456. Cells from a Scraping of the Spleen. (KÖLLIKER.)

- | | |
|---|------------------------------|
| A. Splenic pulp cell containing red blood corpuscles, <i>b</i> (<i>k</i> = nucleus). | E. Giant cell. |
| B. Leucocyte with polymorphous nucleus. | F. Nucleated red corpuscles. |
| C. Pulp cell containing disintegrated red corpuscles. | G. Normal red corpuscle. |
| D. Lymphocyte. | H. Multinuclear leucocyte. |
| | J. Eosinophile cell. |

plethysmograph, and its volume be recorded, it will be seen to be subject to a series of slow variations, each contraction and expansion lasting about a minute and recurring with great regularity (Fig. 455). Superposed on these larger waves are smaller undulations due to the respiratory variations and heart beats.

In spite of these slight contractions, however, the normal pulp circulation is probably very sluggish. Thus Barcroft found that when rats were slowly poisoned with carbon monoxide, it was a long time before the splenic blood, drawn by puncture, became as saturated with CO as that

in the general circulation. The contractile power of the spleen is under the control of the nervous system, and a rapid and extensive contraction may be induced by stimulation of the splanchnic nerves, and also occurs during asphyxia or anoxæmia. Under these conditions, a considerable volume of blood, which is very rich in red cells, is expressed into the general circulation. In the cat, it was estimated that one-sixth of the total blood volume, or one-third of the total red cells, could be so expelled from the spleen.

FUNCTIONS OF THE SPLEEN. Microscopic examination shows us that the reticulo-endothelial cells of the spleen are full of particles of brown pigment or fragments of red corpuscles (Fig. 456), and we have already discussed the destruction of red corpuscles and the formation of bilirubin in these cells (p. 673). The iron liberated from the disintegrated hæmoglobin



FIG. 457. Shrinkage of the Spleen of the Cat with Exercise. Reconstruction from X-ray outlines as seen from the side. (BARCROFT.)

is stored in the reticulo-endothelial cells in some form of combination with other substances.

In many cases of infectious disease, such as recurrent fever, the splenic cells are observed towards the end of the attack to be full of the organism—a spirillum—which is the cause of the disease. In fact, these cells can take up solid particles held in suspension in the blood plasma. We must, indeed, look upon the spleen as the great blood filter, purifying the blood in its passage by taking up particles of foreign matter and effete red corpuscles. It also produces lymphocytes and monocytes, as we have already seen.

Barcroft has shown that the spleen may serve as a reservoir of red blood corpuscles. When there is a deficiency of hæmoglobin in the blood, or of oxygen, the spleen contracts, driving some of the corpuscles it contains into the general circulation. Thus it contracts in exercise, in asphyxia after hæmorrhage, &c., to such an extent that it may be reduced to a fraction of its former size (Fig. 457). No doubt the liberation of adrenaline into the blood also greatly assists the contraction of the spleen under these conditions.

Dale and Dudley have recently shown that the spleen of some animals is particularly rich in esters of choline. Whether the presence of this potent substance has any special significance is at present unknown.

CHAPTER XXXVII

LYMPH, TISSUE FLUIDS, AND CEREBRO-SPINAL FLUID

NOWHERE in the body does the blood come in actual contact with the living cells of the tissues. In all parts the blood flows in capillaries with definite walls, and is thus separated from the tissue-elements by these walls and by a varying thickness of tissue. In some organs, such as the liver and lung, every cell is in contact with the outer surface of some capillary; while in others, such as cartilage (which is quite avascular), a considerable thickness of tissue may separate any given cell from the nearest capillary. A middleman is thus needed between the blood and the tissues, and this middleman is the tissue fluid, or lymph, which fills spaces between all the tissue elements, so that any tissue can be regarded as a sponge soaked with lymph.

Throughout these spaces we find a close network of vessels, lined and separated from the tissue spaces by a layer of extremely thin endothelial cells, and this plexus communicates with definite channels—lymphatics, by which any excess of fluid in the part is drained off. The lymphatics all run towards the chest, where those of the hind limbs join a large vessel (the *receptaculum chyli*), which receives the lymph from the alimentary canal, to form the thoracic duct. This, after receiving the lymphatic trunks from the left fore limb and the left side of the neck, opens into the venous system at the junction of the left internal jugular with the subclavian vein. A small vessel on the right side drains the lymph from the right fore limb and right side of the chest and neck.

The lymph may be looked upon as a part of the plasma which exudes through the capillary wall, bathes all the tissue elements, passes between or through the endothelial cells into the peripheral lymphatic network, whence it is carried by lymphatic trunks into the thoracic duct, by which it is returned again to the blood.

It is easy to obtain lymph for examination by putting a cannula into the thoracic duct, and collecting the fluid that drops from it.

We may also tap in a similar way one of the large lymphatic trunks of the limbs; but in the latter case we have to use artificial means to induce a flow of lymph, since little or none can be obtained from a limb at rest, the only part of the body where there is normally a constant flow of lymph being the alimentary tract. The lymph is thus truly a middleman; as any substance, oxygen or foodstuff, is taken up by a tissue cell from the lymph surrounding it, this latter recoups itself at once at the expense of the blood. Thus there would seem to be no need for lymphatics to drain the limb, were it not that under many conditions, which we shall study directly, the exudation of lymph from the blood vessels is so excessive that, if it were not carried off at once and restored to the blood, it would accumulate in the tissue spaces, give rise to dropsy, and by pressure on the cells and blood vessels affect them injuriously.

PROPERTIES OF LYMPH. Lymph obtained from the thoracic duct of an animal, varies in composition and appearance. From a fasting animal the lymph is a transparent liquid, generally slightly yellowish. When obtained from an animal shortly after a meal, it is milky from the presence of minute particles of fat that have been absorbed from the alimentary canal. In the latter case, if the intestines be exposed, the small lymphatics are to be seen as white lines running from the intestine to the attached part of the mesentery. It is owing to this fact that these lymphatics have received the special name *lacteals*, the lymph in them being called the *chyle*. The fatty particles form the *molecular basis* of the chyle.

On microscopic examination, the transparent lymph of fasting animals presents lymphocytes similar to those of blood, which are partly derived from the lymphocytes that have entered with the lymph through the thoracic duct.

All the lymphatics pass at some point of their course through lymphatic glands, which we may look upon as factories of lymphocytes, since these are much more numerous in the lymph after it has traversed the gland than before. Lymphocytes are also formed in all the numerous localities where we find adenoid tissues, such as the tonsils, air passages, alimentary canal (Peyer's patches and solitary follicles), Malpighian bodies of the spleen, and thymus.

The lymph from the thoracic duct is alkaline, has a specific gravity of about 1015, and clots at a variable time after it has left the vessels, forming a colourless clot of fibrin, just like blood plasma. It contains about 6 per cent. of solid matters, the proteins consisting of fibrinogen, globulin, and serum albumin. The salts are similar to those of the plasma, and are present in similar proportions.

THE PRODUCTION OF LYMPH. A careful investigation of the known experimental facts has failed to show that in the formation of lymph the endothelial cells act otherwise than passively, as filtering membranes of variable permeability. The factors which are responsible for the transudation of lymph may be divided into two classes—mechanical and chemical, the former depending largely on the pressure of the blood in, and the degree of active dilatation of, the vessels, and the latter chiefly on the metabolism of the cells outside the vessels.

If the formation of lymph may be compared to a process of filtration, the amount of lymph formed in any given capillary area must be dependent on the capillary permeability, and on the difference of pressure between the blood in the vessels and the fluid in the extravascular tissue spaces. This latter pressure is normally extremely low, so that we should expect that the lymph production will rise and fall as the capillary pressure is increased or diminished. On attempting to test this hypothesis by experiments in different parts of the body, we have to recognise another factor besides the capillary pressure, viz. the permeability of the vessel wall. Whereas the capillary walls in the limbs and connective tissues generally, present a very considerable resistance to the filtration of lymph through them, and keep back the larger portion of the proteins of the blood plasma, the intestinal capillaries are much more permeable, while in the liver we find the greatest permeability.

The trivial lymph flow from a limb lymphatic is practically unaltered by changes in its arterial supply, although a definite increase may be obtained by ligaturing all the veins of the limb so as to cause a very great rise of capillary pressure. The lymph flow from the intestines can be measured by collecting the lymph from the thoracic duct. If the lymphatics which leave the liver in the portal fissure be previously ligatured, the whole of the thoracic

duct lymph in an animal at rest is derived from the intestines. It will be found that lowering of the capillary pressure in these organs, by obstructing the thoracic aorta, stops the flow of lymph absolutely, whereas a rise of capillary pressure, such as that produced by ligature of the portal vein, causes a four or five fold increase of the lymph. The lymph from the intestines is relatively rich in proteins.

The effect of rise of capillary pressure on the lymph flow is still more striking in the case of the liver. If the inferior vena cava be obstructed just above the opening of the hepatic veins, there is a rise of pressure in the liver capillaries to three or four times the normal height, and a large increase in the lymph flow from the thoracic duct. The lymph may be increased eight to ten times in amount, and it contains more protein than before, in fact almost as much as the plasma. If the portal lymphatics be previously ligatured, obstruction of the inferior vena cava has no effect on the lymph flow, showing that the whole of this increase is derived from the one region of the body where the capillary pressure is increased, viz. the liver.

It is possible to prepare artificial membranes, *e.g.* of collodion, which show similar gradations of permeability; some so slightly permeable that no colloids can be forced through them (*cf.* ultra filtration, p. 107), others allowing some colloids (of small size of particles) to pass, while retaining others, and some even allowing nearly all the colloids of the plasma to pass. When such a collodion membrane is used in an osmometer, with blood plasma inside and water or salt solution outside, the salts and other materials to which it is permeable will pass through, and the only osmotic pressure exerted will be that of the colloids which cannot permeate. Hence the higher the permeability of the membrane, the lower the effective osmotic pressure of the colloids, and the greater the amount of plasma constituents that will pass through. If the pressure inside the osmometer is raised above the osmotic pressure of the retained colloid, fluid and dissolved substances will pass out at a rate proportional to the raised pressure.

In the case of the limbs and connective tissues generally, the second factor, that of permeability, comes more into prominence. The osmotic interchanges between blood and cell, through the intermediation of the lymph, are constantly going on in the normal life of the tissue, and are quite independent of the amount of lymph produced. Thus a gland cell may use up oxygen, calcium, or sugar, and create a deficit of these substances in the layer of lymph immediately surrounding the cell. There is at once a disturbance of the equilibrium, and a flow of these substances from blood to lymph is set up. Such changes can occur with great rapidity. We find, for instance, that if a very large amount (40 grammes) of glucose be injected into the circulation, osmotic equilibrium between blood and lymph is established within half a minute of the termination of the injection. In this case, the rise of osmotic pressure caused by the injection of the sugar at once attracts water from the tissue fluid, and this in its turn from the tissue cells, until the osmotic pressure inside and outside the vessels is the same. By this means the volume of the circulating blood is increased at the expense of the tissues. A process of this character may, however, work under normal circumstances in the reverse direction, and lead to a passage of fluid from blood to tissues and tissue spaces. Every active contraction of a muscle, for instance, is attended by the breaking down of a few large molecules into a number of smaller ones, and this causes a rise of osmotic pressure in the muscle fibre and surrounding lymph, and therefore a passage of fluid from blood to lymph. In the same way, a cell of the submaxillary gland, when stimulated by means of its nerve, pours out a quantity of fluid into the gland

duct. This fluid comes, in the first instance, from the cell itself, but the cell recoups itself from the surrounding lymph, raising the concentration of this fluid, and the difference in concentration thus caused, at once induces a passage of water from blood to lymph. In this passage, the endothelial cells of the capillaries play no part, the whole process being conditioned by changes in the gland cells. We have only to paralyse the gland cells by means of atropine, in order to see that the active flushing of the gland, which accompanies activity, produces merely a minimal increase in the lymph flow from the gland.

The influence of tissue activity in the production of lymph is still better shown in the case of a large gland, such as the liver. Stimulation of this organ, by the injection of bile salts into the blood stream, causes a large increase in the lymph flow from the organ, and therefore in the lymph flow from the thoracic duct.

In many of these instances, it is probable that the permeability of the endothelium is increased when there is active dilatation of the capillaries, as happens when an organ becomes active. Further, the relative insusceptibility

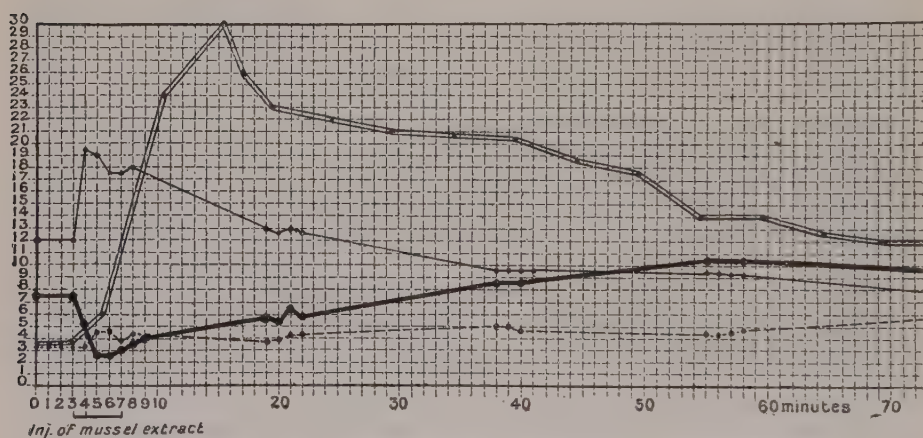


FIG. 458. Changes in Lymph Flow in Portal, Inferior Cava, and Arterial Pressures, resulting from Injection of a Member of the first class of Lymphagogues (Extract of Mussels). The double line = lymph flow in c.c. per ten minutes; thin line = portal vein; thick line = carotid artery; dotted line = inferior vena cava. (STARLING.)

of the limb capillaries to pressure holds only for the absolutely normal capillary. Any factor which leads to impaired nutrition of the vascular wall, such as deficiency of supply of blood or oxygen, the presence of poisons in the blood or in the surrounding tissues, scalding or freezing, increases at the same time its permeability. Under such conditions, the limb capillary reacts to changes of pressure like a liver capillary, the slightest increase of pressure causing an appreciable increase in the lymph production. This increased lymph production may be too great to be carried off by the lymphatic channels, so that the exuded fluid stays in the tissue spaces, distending them, and causing the condition known as *œdema* or dropsy.

LYMPHAGOGUES. Among the substances which have a direct action on the vessel wall, are a number of bodies which were described by Heidenhain as lymphagogues of the first class. As their name implies, these bodies, on injection into the blood stream, cause an increased flow of lymph from the thoracic duct (Fig. 458). They may be extracted from the dried tissues of crayfish, mussels, or leeches by simple boiling with water. Commer-

cial peptone has a similar effect. Their effect on lymph production is probably due simply to their deleterious action on the capillary wall. Although these bodies act chiefly on the liver capillaries, they can be shown also to have some effect in the same direction on the intestinal and skin capillaries. In fact, the injection or ingestion of these bodies often gives rise to a copious eruption of nettlerash due to an increased exudation of lymph into the meshes of the cutis. Histamine, which is present in most tissue extracts, has a similar effect.

An increased lymph flow from the thoracic duct may be produced also by the injection of large amounts (10 to 40 grammes) of innocuous crystalloids,

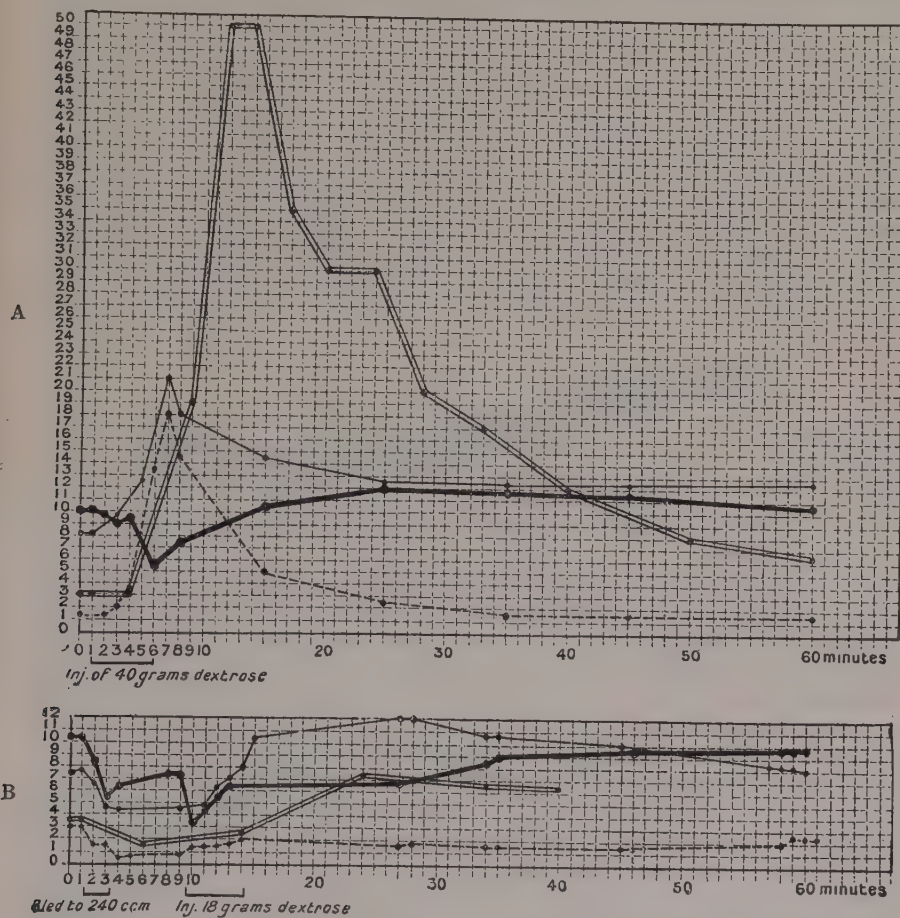


FIG. 459. Effect on Lymph Flow and on Arterial and Venous Pressures of Injection of Concentrated Solution of Glucose.

In B the animal was bled to 240 c.c. before the injection. (STARLING.) Curves indicated as in Fig. 458.

such as glucose, urea, or sodium chloride, into the circulation. In this case the lymph becomes much more dilute. The explanation of the action of these bodies is very simple. We have already seen that after the injection of large amounts of glucose into the circulating blood, a condition of hydraemic plethora is brought about. This increase in the total volume of the blood has two consequences; first, the colloidal osmotic pressure of the plasma proteins is lowered owing to dilution, and second, there is an increased capillary pressure (Fig. 459, A). That the action of these bodies is purely

mechanical is shown by the fact that, if the rise of capillary pressure be prevented by bleeding the animal immediately before the injection, the increase in the lymph flow is also prevented (Fig. 459, B).

MOVEMENT OF LYMPH. In the frog, the circulation of lymph is maintained by rhythmically contracting muscular sacs, which pump the lymph into the veins. In the higher animals, the onward flow of lymph is effected partly by the pressure at which it is passed out into the interstices of the tissues, but also to a large extent by the contractions of the skeletal muscles. In the smaller lymph radicles the pressure of lymph may attain 8 to 10 mm. soda solution. In the thoracic duct, at the point where it opens into the great veins of the neck, the pressure is obviously about the same as in these veins, that is to say, from — 4 to 0 mm. Hg, the negative pressure being occasioned by the aspiration of the thorax. This difference of pressure is sufficient to cause a certain amount of flow. It must be remembered, however, that under normal circumstances no lymph at all flows from a resting limb. The only part of the body which gives a continuous stream of lymph during rest is the alimentary canal, the lymph of which is poured out into the lacteals, and thence makes its way through the thoracic duct. Movement, active or passive, of the limbs at once causes a flow of lymph from them. Since the lymphatics are all provided with valves (Fig. 460), the effect of external pressure on them is to cause the lymph to flow in one direction only,

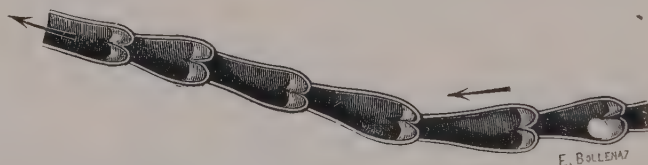


FIG. 460. A Lymphatic Vessel laid open to show Arrangement of the Valves. (TESTUT.)

viz. towards the thoracic duct and great veins. Hence we may look upon muscular exercise as the greatest factor in the circulation of lymph. The flow of lymph from the commencement of the thoracic duct in the abdominal cavity to the main part of it in the thoracic cavity is materially aided by the respiratory movements; since, with every inspiration, the lacteals and abdominal part of the duct are subjected to a positive pressure, and the intrathoracic part of the duct to a negative pressure.

THE ABSORPTION OF LYMPH AND TISSUE FLUIDS. On injecting a coloured solution, or a fine suspension, into the connective tissues of any part of the body, and gently kneading the part, it is found that the fluid fills all the lymphatic channels running from the part; and we can in this way inject the lymphatics of the limb, and trace their course on to the thoracic duct. The same path is taken by micro-organisms as they spread in the tissues, or by particles of carmine or Indian ink which have been introduced in tattooing.

This process of lymphatic absorption, except in the case of the pleural and peritoneal cavities, is a slow one, unless aided to a large extent by passive or active movements of the surrounding parts, and cannot therefore account for the rapid symptoms of poisoning which supervene within two or three minutes after the hypodermic injection of a solution of strychnine or other poison. That this absorption is not dependent on the lymphatics, is shown by the fact that the symptoms occur almost as quickly when all the tissues of the limb have been severed, with the exception of the main artery and vein. In the same way, after injecting methylene blue or indigo carmine

into the pleural cavity or subcutaneous tissues, the dyestuff appears in the urine long before any trace of colour can be perceived in the lymph flowing from the thoracic duct. The absorption in these cases is by the blood capillaries, and consists in an interchange between blood and extravascular fluids, by diffusion. So long as any difference in composition exists between the intra- and extravascular fluids, so long will diffusion currents be set up, tending to equalise this difference.

More difficulty is presented by the question of the mechanism of absorption, into the blood vessels, of the normal tissue fluids—such an absorption as we have seen to occur after loss of blood by hæmorrhage. It seems probable that this absorption depends on the small proportion of protein contained in the tissue fluid as compared with the blood plasma, and is due to the osmotic pressure of the protein. Thus, we may conceive that there is normally a balance in the capillaries between the processes of exudation and of absorption, the former being conditioned by the capillary blood pressure and the latter by the difference in protein content, and therefore of colloidal osmotic pressure, between the blood plasma and tissue lymph. A rise of capillary pressure will upset this balance in favour of transudation, and the blood will become more concentrated; whereas a fall of pressure will turn the scale in favour of absorption, and the volume of blood will be increased at the expense of the tissue fluids.

THE CEREBRO-SPINAL FLUID

Four membranes are interposed between the bony wall of the cranial cavity and the brain itself. From outside inwards, these are: (1) the periosteal layer of the dura mater; (2) the meningeal layer of the dura mater; (3) the arachnoid mater, and (4) the pia mater. The cerebro-spinal fluid lies in the space between the arachnoid mater and the pia mater.

The dura mater consists of firm fibrous tissue; its outer part represents the periosteum, and this is firmly attached to the interior of the cranium. Fibrous partitions are sent from the dura mater into the cavity of the cranium, thus supporting the chief parts of the brain. One of these, the *falx cerebri*, lies between the two cerebral hemispheres. A second, the *tentorium cerebelli*, forms a horizontal division between the cerebral hemispheres and the cerebellum. A third one, the *falx cerebelli*, passes a short distance in between the cerebellar hemispheres. In the spinal canal, the bones have their own periosteum, and the dura mater, which is closely attached round the margins of the foramen magnum, forms a loose sheath round the spinal cord. Tubular prolongations are formed where each nerve-root emerges, and are continuous with the outer sheaths of the nerves. Where the venous sinuses occur, the two layers of the periosteum separate, so that the venous sinus lies between them. These sinuses are angular clefts, the chief of which lie along the attached margins of the *falx cerebri* and the *tentorium cerebelli*. The greater part of the blood which these contain drains into the internal jugular veins. In the spinal cord, these venous sinuses are replaced by plexuses of thin-walled veins, which are embedded in fat and lie on the outside of the dura. The arachnoid is a delicate, transparent membrane, covering the whole of the brain and spinal cord. Superficially it is covered by a layer of endothelial cells which bounds the sub-dural space. On its deep surface, it is connected with the pia mater with numerous fine fibres. It bridges over the inequalities in the surface of the brain, so that spaces are left which are filled with cerebro-spinal fluid. The arachnoid surrounds the cerebral and spinal nerves, and encloses them in loose sheaths as far as their

points of exit from the skull and vertebral canal. On the upper surface of the brain it is very thin; at the base it is thicker. The spinal part of the arachnoid is thin and delicate. It consists histologically of white fibrous and elastic tissue intimately blended, and contains blood vessels and a rich plexus of nerves. Wherever it comes in contact with cerebro-spinal fluid it is covered by flattened polygonal mesothelial cells.

The pia mater is a layer of connective tissue which serves to carry the blood supply to the whole surface of the brain. It closely follows all the irregularities of the latter, dipping down into the fissures and sulci of the brain. In the spinal canal, the pia mater sends out a series of processes, the *ligamentum denticulatum*. The outer extremities of these are attached to the dura mater, and help to sling the spinal cord in its dural sheath. By means of the rich blood supply conveyed by the pia mater, the brain is abundantly supplied with blood. The two carotid and two vertebral arteries convey the blood into the cranial cavity. The vertebrals unite to form the basilar artery, which divides again into two branches, and these unite with branches of the internal carotid arteries to form the circle of Willis. From this circle, three main arteries on each side pass to supply separate regions of the brain, two anterior, two middle, and two posterior cerebral. The inner parts of the brain, *e.g.* corpus striatum, are supplied by branches of the circle of Willis which pass straight into the brain substance. The anastomosis between vessels appears to be very slight. In consequence, if any one vessel becomes obstructed, the blood supply of a considerable brain area may be cut off.

THE SUB-ARACHNOID CISTERNE. The sub-arachnoid cavity, which is the space between the arachnoid mater and pia mater, contains the cerebro-spinal fluid and the larger blood vessels of the brain. It is traversed, as we have said, by spongy tissue consisting of delicate trabeculæ, which run from arachnoid mater to pia mater. In most parts of the cranial cavity, the space thus formed is small; in certain parts near the base of the brain, however, the arachnoid is separated from the pia mater by wide intervals which communicate freely with one another and are named the sub-arachnoid cisternæ. The whole of these cavities, which contain the cerebro-spinal fluid, are completely lined by a continuous sheet of flattened polygonal mesothelial cells.

THE CHOROID PLEXUSES. These plexuses, which are found lying in the ventricles of the brain, consist of highly vascular tufts which are covered by ependymal cells. These peculiar masses of tissue apparently form the cerebro-spinal fluid. Evidence of the secretory nature of these choroid plexuses is partly of a histological, and partly of an experimental, nature. The cells are seen to contain granules, both eosinophil and basophil. Pilocarpine, which generally stimulates glands into activity, is found to exert a pronounced effect on the ependymal cells, so that the protoplasm of the cell becomes greatly increased in amount. The experimental evidence is, that if, by blocking the foramen of Monro, one of the ventricles is prevented from getting rid of the fluid secreted into it, then hydrocephalus develops in that particular ventricle. Such a process does not take place if the choroid plexus be first removed from the ventricle (Weed).

THE ARACHNOID VILLI. These are minute processes of the arachnoid which are found to project into the venous sinuses. Where these projections occur, the dura mater is interrupted. The processes themselves are lined by two layers of cells. Externally they are covered by the endothelium of the cerebro-venous sinuses, and internally by the mesothelial cells of the arachnoid mater. They are present in most animals, as well as in men of all ages. They are present in most of the cerebral sinuses, and are occasionally found penetrating the dura in other regions.

THE PERIVASCULAR SPACES. Surrounding each of the blood vessels which penetrates into the surface of the central nervous system, is a sleeve formed of mesothelial cells. These are called perivascular spaces. Thus a path is left clear for fluid to escape from the cell spaces inside the brain substance into the cerebro-spinal space. If these perivascular channels are followed inwards, they terminate in what are called perimural spaces. These may vary considerably in size, and were originally considered to be parts of a lymphatic system.

THE CEREBRO-SPINAL FLUID. The chemical composition of this fluid is rather like that of lymph. Its specific gravity is about 1005. It contains salts, glucose and a little protein. Its total quantity in man is about 150 c.c. Its pressure inside the cranial cavity is 100 to 120 mm. of water. Urea and creatinine are present in small amounts. In health the number of cells which it contains is extremely small. In diseases of the brain, marked changes in the chemical composition of the cerebro-spinal fluid may take place. The protein content may increase, and cells may appear in large numbers. When the infections are tubercular, the cells are principally lymphocytes; in other types of infection they are principally leucocytes. In renal disease, chlorides are increased.

CIRCULATION OF CEREBRO-SPINAL FLUID. This originates from two sources, the choroid plexuses in the ventricles, and the perivascular spaces found in relationship with the vessels of the pia mater. It flows from the ventricles by way of the foramen of Monro into the third ventricle, and thence by the aqueduct of Sylvius, it reaches the fourth ventricle, from which it escapes, by way of the foramina of Majendie and Luschka, into the sub-arachnoid space. Having originated in this manner, the cerebro-spinal fluid passes slowly towards the convexity of the cerebrum to reach the arachnoid villi, and to pass into the venous sinuses. That this is the normal direction taken by the circulation has been amply proved by Weed. Under certain circumstances, it is possible to reverse the normal direction of flow. Instead of cerebro-spinal fluid being produced in the perivascular spaces, as is normally the case, in cerebral anæmia the spaces may be widely dilated and absorption of cerebro-spinal fluid may take place there, presumably into the capillaries and veins.

CHAPTER XXXVIII

THE DEFENCE OF THE ORGANISM AGAINST INFECTION

THE CELLULAR MECHANISMS OF DEFENCE

IN most cases, invasion of a higher animal or plant by some lower organism is fraught with danger to the host, so that special mechanisms have to be provided for the protection of the tissues from infection. There are four types of lower organism against which defence is needed, viz. *viruses* (e.g. measles, small-pox), *bacteria* (e.g. tetanus, diphtheria), *moulds* (e.g. ringworm), and *protozoa* (e.g. malaria, syphilis, amœbic dysentery). The most primitive means of defence, and one which is found throughout the whole animal kingdom, is exactly analogous to the process by which the amœba destroys and utilises any bacteria present in its environment.

The prevention of infection is of course the function of the epithelial covering, either of the skin, or of the surface of the gut. Protection here may be of a physical or chemical character. The cells may secrete a horny or chitinous layer, which presents a mechanical obstruction to the entry of bacteria. They may secrete mucin, which entangles and hinders the movements of invading micro-organisms, or they may secrete substances which actually destroy the life of such organisms.

When, however, a micro-organism has obtained entrance to the interior of the body, e.g. through a wound of the surface epithelium, the task of dealing with the invader becomes the office of a special type of cells called *phagocytes*, and the whole process by which foreign material, or the animal's own dead tissues are got rid of, is spoken of as *phagocytosis*. The process of phagocytosis may be studied in its simplest form by injuring or infecting some tissue which is free from blood vessels. Thus, the tail fin of an embryonic axolotl may be cauterised with silver nitrate, or a small quantity of fluid containing carmine granules may be introduced by means of a hypodermic syringe. In either way a certain number of cells are destroyed, and the dead tissue thereupon is treated as a foreign body. As a result, the wandering cells or histiocytes (macrophages) move from the surrounding tissues towards the seat of the injury, and the day after the injury has been inflicted, a collection of these macrophages can be seen, many of which contain particles of carmine, or débris of the destroyed tissue, which they have taken up. The cells finally wander away from the part, and the destruction is made good by the proliferation of the fibroblasts, and of the epithelium immediately adjoining the injury.

By the vascular system, all the tissues of the body are brought into material relationship with one another, so that many distant parts may be drawn upon to supply the needs of any one part. It is evident that the accumulation of cells for the defence of the organism against invading microbes, will be much more effective if the blood vessels participate in

the process, so that, by their means, the phagocytic resources of all parts of the body can be drawn upon to ward off a localised attack. The process of phagocytosis thus, in the higher animals, becomes merged into the more complex series of phenomena to which the term 'inflammation' has been applied. This process can be studied by observing the effects of slight injury to some vascular transparent part of the body, *e.g.* the frog's tongue or mesentery, or the web of the frog's foot. For this purpose a small piece of the skin of the frog's web may be snipped off with fine curved scissors, the section being sufficiently deep to remove the skin without causing hæmorrhage. The first effect noticed in the immediate neighbourhood of the injury is a dilatation of the vessels, especially of the venules, and an acceleration of the blood flow. In the course of an hour, the capillaries also become dilated, and many capillary channels, previously invisible, are now occupied with blood. In some instances, in higher animals, new capillaries have been observed, under the microscope, to grow out from other capillaries, towards the area of inflammation. Through the dilated capillaries there is a rapid blood stream, the corpuscles occupying the axis of the vessel, so that there is a periaxial layer of plasma. A little later, this acceleration gives place to a slowing of the blood stream, and simultaneously the leucocytes of the blood are seen to be adherent to the capillary wall. Apparently the latter becomes what we may call 'sticky,' the effect of the stickiness being to increase the resistance to the passage of the blood through the vessel, and also to cause the adhesion of the leucocytes to the wall. As the current becomes still slower, the distinction between axial and peripheral streams disappears. The corpuscles are now closely packed together, the white corpuscles being predominant at the margins of the capillary, where they form a lining to the vessel (Fig. 461). The next stage is the emigration of the leucocytes.

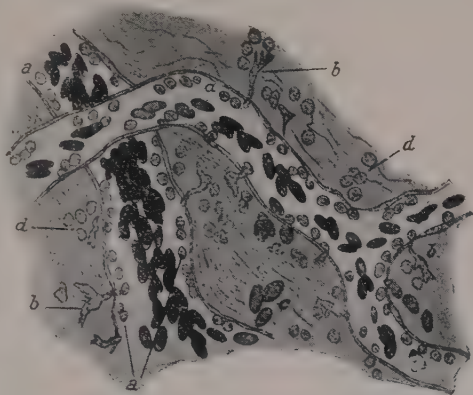


FIG. 461. Inflamed Mesentery of Frog, to show margination of leucocytes in the inflamed capillaries, *a*; migration of leucocytes, *b*; escape of red corpuscles, *c*; accumulation of leucocytes outside the capillaries, *d*.
(From ADAMI after RIBBERT.)

These may be observed to thrust a process through the vessel wall (according to Arnold this process of emigration always occurs through the stigmata, *i.e.* the points where the endothelial cells come in contact—Fig. 462). The prolongation enlarges on the outer side of the vessel, while the portion of the leucocyte within the vessel becomes smaller, so that finally the whole leucocyte passes through, and lies in the lymph spaces outside the capillary. In the course of five or six hours, all the capillaries and small veins in the neighbourhood of the injury may show a crowd of polymorphonuclear leucocytes along their outer surfaces. In addition, there is a migration of certain tissue cells, *viz.* fibroblasts and histiocytes, to the affected place; later, there is often a further emigration from the blood of histiocytes and of lymphocytes. Of these various cells, the polymorphonuclear leucocytes and the histiocytes are phagocytic, and help to remove invading particles or organisms, and also later to remove the tissue injured by the

primary lesion. As soon as this is effected, regeneration of the injured tissue occurs by a proliferation of the fibroblasts and the epithelium, while the leucocytes move away and disappear.

Inflammation in warm-blooded animals thus gives rise to dilatation of vessels and increased vascularity of the part, to alteration of the vessel wall and therefore to increased effusion of fluid. There are warmth and redness



FIG. 462. Emigration of Leucocytes through Capillary Wall. (ARNOLD.)

of the part from the vascular dilatation, swelling from the effusion of lymph, and very often, as a result of the injury or the swelling and the consequent involvement of sensory nerves, pain. The four cardinal symptoms of inflammation, namely, *rubor*, *calor*, *tumor*, and *dolor*, which have been described for generations as typical of this condition, leave out of account altogether the phenomenon of phagocytosis round the seat of injury with the objects of destroying micro-organisms, of protecting the body from general infection, and of preparing the way for reintegration of tissue.

The essential phagocytic character of the inflammatory process is clearly shown if the primary lesion be attended with infection. Thus, if a small quantity of a culture of staphylococcus be injected into the subcutaneous tissue of the rabbit, the vessels surrounding the point of injection may, within four hours, be found densely filled with corpuscles. In ten hours' time the leucocytes are present in large numbers outside the vessels, while the injected cocci have spread for some distance along the lymphatic spaces and, while still partly free, have been to a large extent ingested by the leucocytes. In twenty hours' time the connective tissue fibrils at the point of injection are found to be widely separated by the aggregation of phagocytes. In forty-eight hours' time a well-defined abscess is produced. At the centre of this, all traces of previous connective tissue have disappeared and its place has been taken by *pus*, i.e. a mass of leucocytes, many of them dead and in a state of degeneration, mingled with staphylococci, partly within, partly outside the cells. The margin of the abscess is formed by connective tissue infiltrated with living leucocytes. A certain number of cocci are to be seen free in the tissue outside this layer, but in the course of a day or two these free cocci disappear, and there is thus a continuous layer of phagocytes surrounding the abscess cavity, and preventing any further invasion of the body as a whole from the seat of infection. The abscess subsequently discharges on to the exterior by a process of necrosis of the superjacent skin, and regeneration of tissue takes place in the same manner as in the more trivial injury.

We have abundant evidence to show that the essential factor in this aggregation of leucocytes is their chemical sensibility, and that the phenomenon is simply one of *chemiotaxis*. A capillary glass tube containing a suspension of dead micrococci, or peptone, or broth extracted from dead tissue, if introduced into the anterior chamber of the eye or into the subcutaneous tissue, is found after a short time to be full of leucocytes. We must assume that the chemical products diffusing out of the ends of the capillary tube have occasioned a positive chemiotaxis on the part of the leucocytes. It is worthy of note that the positive chemiotactic influence exerted by any given species of pathogenic bacterium is roughly inversely proportional to its virulence. A culture lacking in virulence may cause a very pronounced aggregation of leucocytes which speedily ingest and destroy the micro-organism, whereas

if a culture of a more virulent variety of the same microbe be injected, there may be all the signs of inflammation, swelling, and large effusion of fluid, though the tissues may contain very few leucocytes. Under the circumstances, the micro-organism rapidly proliferates and spreads from the seat of the lesion, giving rise finally to general infection.

The part played by each of the types of cell involved in the inflammatory reaction is still to a large extent the subject of discussion. There is no doubt that, in all active inflammations, the polymorphonuclear leucocyte is the form which is attracted first, and in largest numbers, to the seat of injury. It is the characteristic cell from which pus is formed, and is actively phagocytic. It has nothing to do with the regeneration of the destroyed tissue. The eosinophile corpuscle is also present at an early stage around the inflammatory focus, but is never present in numbers at all comparable with those of the polymorphonuclear leucocyte. It is especially abundant in chronic inflammations of certain tissues, such as the skin, but is rarely seen to ingest bacteria, and therefore cannot be spoken of as phagocytic. The lymphocyte predominates in certain chronic inflammations, especially in those caused by the tubercle bacillus. They do not ingest bacteria. The histogenous wandering cells (macrophages) appear in the inflammatory area at a later period than the polymorphonuclear and eosinophile cells. They are actively phagocytic and motile. As a rule, their phagocytic properties are exerted, not on bacteria, but on other cells and cell *débris*. After an acute inflammation, their chief office is to clear away the remains of the polymorphonuclear leucocytes and dead tissues, so as to prepare the way for subsequent regeneration. The fibroblasts are immature forms of connective tissue cells, and it is held by some investigators that they can be converted into macrophages, and *vice versa*. It is, however, difficult to be certain whether the wandering and the fixed connective tissue corpuscles are of identical or of different origin. In the process of repair, the fibroblasts are converted into fibrous tissue.

We thus see that several types of the wandering cells of mesoblastic origin, which take part in inflammation, do not exert active phagocytic properties and cannot therefore destroy bacteria or other invading organisms by the process of ingestion and digestion. Yet we have evidence that the part played by such cells in the defence of the organism is no less important than that of the actively phagocytic cells. Leucocytes are able to destroy bacteria, not only by the process of intracellular digestion, but also by the excretion, into the surrounding body-fluids, of substances which have a deleterious influence on bacteria. Thus, normal blood serum is found to have a strong destructive influence on most species of bacteria, whether pathogenic or not. Since this property is not shared to anything like the same extent by the blood plasma, it may be ascribed to the breaking down of leucocytes in the process of clotting and the consequent liberation of bactericidal substances. Many species of pathogenic bacteria cannot infect the animal as a whole. These, nevertheless, may multiply on the surface of the body, or in an abscess cavity, and lead to the death of the host, in consequence of the production by the bacteria of soluble *toxins*, which are absorbed into the blood stream. Examples of such micro-organisms are those which are associated with tetanus and diphtheria. There must be other mechanisms at the disposal of the body for the neutralisation of these toxins. The protection of the body against destruction by bacterial toxins involves in fact a whole series of chemical mechanisms, which we must regard as of equal importance and as co-operating with the phagocytic mechanism.

THE CHEMICAL MECHANISMS OF DEFENCE

INFECTION AND IMMUNITY. All infectious diseases are caused by the agency of micro-organisms. The greater number of these are bacteria, a certain number must be classed with the yeasts, while others are protozoal in character.

In the protozoal diseases the micro-organisms occur for the greater part as intracellular parasites. One attack of the disease does not as a rule confer immunity, and the treatment has to be sought along the lines of medication by drugs, which will either directly destroy the infecting agent, or enable the tissue to combat it. It is especially in the first class of diseases, namely, those due to bacteria, that the organism has developed chemical mechanisms of defence.

The diseases due to bacteria include diphtheria, tetanus, tubercle, anthrax, pyæmia, and many others. In these diseases we have to deal with a number of phenomena more or less common to all. The infection in each case is due to the actual transference of the specific organism from one animal to another. After the micro-organism has attained entrance into the system there is a period of incubation before the disease actually breaks out. When this occurs, the specific microbe is to be found in large quantities either in the blood or in the tissues of the body. The disease is generally characterised by fever and often by local lesions, such as the intestinal ulcers of typhoid, or the glandular swellings of bubonic plague. The micro-organisms may develop in the animal until its death, or the disease may terminate in recovery and the total disappearance of the microbes from the body. Some animals or individuals are naturally immune to particular diseases, *e.g.* dogs to typhoid, and this is called *natural congenital immunity*. In other cases, it is found that, after recovery, the patient is protected from reinfection by the bacterium which was the cause of the disease, and this condition, called *natural acquired immunity*, may last as long as the patient lives.

The infections due to the viruses are in many ways similar to those induced by bacteria, but in this case the causative organism is so minute that it can pass through the pores of the finest filter, and is invisible under the microscope. Moreover, the viruses cannot be cultivated outside the living body, whereas the pathogenic micro-organisms can, usually, be cultivated on artificial media outside the body, and may be divided into two classes.

TOXINS. One class, of which the diphtheria and tetanus bacilli are examples, secrete into the surrounding culture-fluid substances, which, when injected into animals, act as virulent poisons. The other class of bacteria do not form such extracellular toxins, but in their case it is found that, if the bodies of the bacilli be broken up, the injection of the contents of the bacteria is attended with poisonous effects. The bacteria may be thus classified according as they produce extracellular or intracellular toxins.

We may first deal with the manner in which the body reacts to the exotoxins. If a culture of diphtheria or tetanus bacilli be filtered, the clear filtrate free from bacilli is found to exercise as poisonous results as if the culture itself of the living bacilli had been employed. The toxins contained in these fluids are extremely potent. Thus five-millionths of a gramme of dried tetanus toxin is a fatal dose for a mouse, and 0.00023 gramme would kill a man; the pure toxins, which have never been isolated, must be even more powerful. The toxin is an unstable body, and is destroyed by heating to 65° C. The nature of toxins is not known, though they probably contain proteins. Similar toxins are widely distributed throughout the vegetable and animal kingdoms. Thus they form the active constituent of snake venom and of the poison of

scorpions and spiders. They also occur in the seeds of castor oil and of jequirity, the toxins of which seem to be of a protein character and are known respectively as *ricin* and *abrin*. There is a great variability in the reaction of different animals to these toxins. To the poison of tetanus, the rabbit is, weight for weight, two thousand times, and the hen twenty thousand times, more resistant than the guinea-pig. A certain time is necessary after the introduction of the toxin before its effects are displayed. There is a striking difference in this respect between the action of these complex bodies and the action of drugs, such as strychnine or morphine. This time cannot be reduced beyond a certain limit, however much toxin be injected. Thus, a lethal dose of diphtheria toxin kills a guinea-pig in fifteen hours. If ninety thousand such doses be injected into a guinea-pig, it is not possible to reduce the time of survival below twelve hours. Another characteristic of these toxins is the specificity of their action. One kind of toxin may act chiefly on the central nervous system, another on the peripheral nerves, another on the red blood corpuscles. Associated with this specific action is the actual combination which occurs between the toxin and the organ on which it exerts its effect. Thus, tetanus toxin has a specific affinity for the central nervous system, and may be removed from a solution by shaking the latter with an emulsion of the brain of a susceptible animal, such as a guinea-pig, but not with one of the brain of an animal of a non-susceptible species.

ANTI-TOXINS. In spite of the excessively fatal character of these toxins, it is possible to render an animal immune to their action. If a dose of diphtheria or tetanus toxin which is smaller than the fatal dose be injected into an animal, the latter may show signs of injury, from which it recovers. When recovery is complete, it is found that three or four times the fatal dose may be injected without producing any evil effects; and this process of injection of toxin may be repeated in continually increasing doses, until the animal may finally be able to withstand a dose one hundred thousand times as large as that which would have been fatal to it in the first instance. This is a condition called *active artificial immunity*, and it is found that the blood serum of the immunised animal has the power of neutralising the toxin. Thus, if blood serum from a horse which has been treated with large doses of diphtheria toxin be mixed with an equal quantity of the toxin itself, the mixture may be injected into susceptible animals without the production of any effect. It is possible in this way to get a serum, 1 c.c. of which will neutralise many fatal doses of the toxin; further, this antitoxic serum may be injected into a susceptible animal and then confers *passive artificial immunity* on the latter, or it may be injected into a diseased animal and so used as a curative agent. *Antitoxins* thus play a great part in modern therapeutics, especially of diphtheria. In the case of tetanus, the toxin has a specific affinity for the nervous system and apparently travels up the axis cylinders of the nerves to the central nervous system. By the time that it has arrived at the central nervous system, and the spasms typical of tetanus have broken out, the toxin is already so firmly bound to the reacting tissue that the injection of antitoxin into the blood stream has little or no effect on the course of the disorder. The use of the tetanus antitoxin is, therefore, chiefly as a prophylactic agent.

If we define a unit of toxin as that amount which possesses a certain power, *e.g.*, which will kill a guinea-pig in so many days, or will cause the complete hæmolysis of 1 c.c. of blood in two and a half hours, we can find the amount of anti-body which is just sufficient to neutralise this effect, and this amount of anti-body can be regarded also as one unit. If, instead of one unit of each, we take 100 units, the neutralisation is effected in the same way. The process is found, however, to be more complex when we take 100

units of toxin, or lysin, and attempt to neutralise them by the fractional addition of antitoxin. In the case of a strong acid and strong alkali, we know that if 100 c.c. of alkali are just sufficient to neutralise 100 c.c. of acid, the addition of 50 c.c. of alkali will leave half the acid unneutralised. If we try the same experiment in the case of mixtures of toxin and antitoxin, it will be found that the addition of 50 units of antitoxin will neutralise much more than half of the toxin, and the same applies to other bodies of this class. Further, 1 c.c. of antilysin exactly neutralises 1 c.c. of lysin; but these two substances will no longer be in equilibrium when the whole is diluted up to 10 c.c. with water.

The interaction, therefore, is probably a special example of adsorption, like the adsorption of iodine from solutions by charcoal, of iodine from water by starch, or of ammonia by charcoal. The exact adsorption which takes place must be a function of the chemical configuration of the substance forming the surface, since otherwise it would be impossible to account for the extremely specific character of the interaction between toxins and their corresponding antitoxins. The interaction must, therefore, be assigned to that special class, in which we have already placed the action of enzymes, which is not entirely chemical nor entirely physical, but depends for its existence on a co-operation of both chemical and physical factors. In any case, the antitoxin does not destroy the toxin, since it is possible, from an inert mixture of toxin and antitoxin, to separate toxin and anti-body once more.

THE SIDE-CHAIN THEORY. How are we to account for the production, as a result of the injection of toxins into the body, of antitoxin far transcending the amount of toxin injected? In all the speculations on the mode of production and action of antitoxins, an important part has been played by a conception put forward by Ehrlich in 1885. According to this conception, which is spoken of as the 'side-chain theory,' each unit of living matter consists of a centrally placed portion with a number of 'side chains' attached to it. To these side chains, or *receptors*, various nutritive or other substances may be linked, provided their chemical configuration is of the right kind. Ehrlich regarded the toxins as possessing two side chains, one of which, by its stereomeric configuration, is peculiarly adapted to fit on to the same side chains of the protoplasm as those which the toxin attacks, and is known as the *haptophore* group; and another side chain, the *toxophore* group, which is responsible, when the toxin is once anchored, for the destructive changes wrought by the toxin on the cell of the body (Fig. 463, 2). The antitoxins are supposed to act by uniting with the haptophore group, and so preventing the susceptible protoplasm from doing so and exercising their injurious effects on the body.

The formation of antitoxins is accounted for on this hypothesis in the following manner. When a receptor of the cell is occupied by becoming attached to the haptophore group of the toxin, this side chain is, so to speak, shut out from the normal activities of the cell. A defect is thus produced in the cell, to which the latter endeavours to adapt itself by the production of other side chains of the same character (Fig. 463, 3, 4). It may be regarded as a general rule in living tissues, that a reaction tends to be an over-reaction, so that the compensation by the cell should more than make good the defect produced by the attachment of the toxin. We thus get, not one, but a number of side chains produced, of the same character as that occupied by the toxin molecule, and therefore able also to act as receptors for the haptophore group of the toxin. These new receptor side chains, being produced in excess, are supposed by Ehrlich to be thrown off from the cell and to circulate in the body fluids (Fig. 463, 4). A number of protoplasmic fragments are thus set free which have a specific power of uniting with the toxin, and it is this excess of side chains, thrown off from the cell, which represents the antitoxin molecules found circulating in the blood after the injection of toxins. It will be noted that this theory, though chemical in form, is really purely biological. It does not explain the phenomena by reference to the known laws of chemistry, but is a manner of viewing the biological phenomena, which facilitates their description and discussion and enables us to classify the very complex phenomena of immunity, though only in an imperfect fashion.

ANTIGENS. The property of giving rise to anti-bodies on injection into an animal is not confined to toxins; a large number of substances, all of them containing proteins, have the same property. All such substances are classed together as *antigens*, and are highly specific. Thus, bacteria, alive or dead (and thus including endotoxins), or any animal or vegetable cells, venoms, viruses, or pure proteins derived from any of them, can act as antigens, pro-

vided they are foreign to the species of animal into which they are injected. They all give rise to the production of *specific anti-bodies*. Thus, human serum injected into a rabbit produces in a few days in the rabbit's serum some body which will give a precipitate when mixed with human serum even in minute traces. This *precipitin* formation is specific, so that it may be used as a test for the origin of any unknown specimen of serum.

In a similar way, using an extract of dead bacteria, or any protein, as antigen, a specific precipitin for the bacterial extract or for the particular protein, as the case may be, develops in the blood.

A *vaccine* is such a collection of killed bacteria or virus, and is often injected into patients to stimulate the production of anti-bodies.

When live foreign cells, e.g. bacteria or red cells, are injected, there is developed an

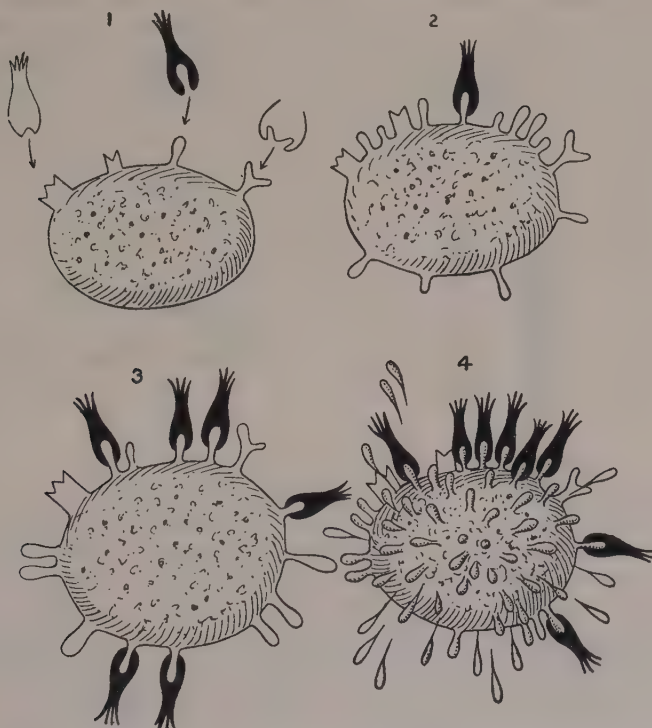


FIG. 463. Schematic Representation of Formation of Antitoxin as Side Chains of Protoplasmic Molecule. The black bodies are the toxin molecules which fit by their haptophore end on to the side chains of the cell. (EHRlich.)

anti-body which causes these cells, when added to the serum, to gather together or agglutinate. Typhoid fever can be diagnosed by the fact that the patient's serum causes agglutination of the bacteria in a pure typhoid culture (Widal test). The anti-body concerned is called an *agglutinin*.

The nature of these specific anti-bodies, and the cause of the high specificity to the antigens which give rise to them, are not exactly known. As regards antitoxins, these have never been obtained free from proteins, and it is likely that much of their specificity is due to them. With regard to the antigens of bacteria, recent work has indicated that, while some of the specificity is attributable to proteins, the most specific immunological reactions are often associated with the presence of highly specialised carbohydrates, as well as proteins.

CYTOLYSINS. We have already seen that normal blood serum may exert a paralytic or destructive action on bacteria. Light has been thrown

on the factors involved in this destruction by a study of the phenomena which result when living cells are injected. Normal goat's serum may be mixed with the red blood corpuscles of the sheep without any injury to the latter. If, however, washed sheep's corpuscles be injected at intervals of a few days into a goat, the goat's serum is found to have acquired the power of rapidly agglutinating, and then of dissolving, the red blood corpuscles. A specific *hæmolyisin* is said to have been produced. This hæmolytic power can be tested by mixing the serum and the washed blood corpuscles together and allowing the mixture to stand in a narrow tube. The corpuscles rapidly sink to the bottom, leaving the colourless serum above, unless hæmolysis has occurred, in which case the serum will be of a transparent red colour.

If the hæmolytic serum be heated to 55°C . it is found to have lost its power of dissolving sheep's corpuscles. This power is at once restored if to the heated serum be added any normal blood serum, even of the sheep itself. It seems, therefore, that two substances are involved in the hæmolysis, namely, (a) a substance present in most normal sera, and believed to be formed by

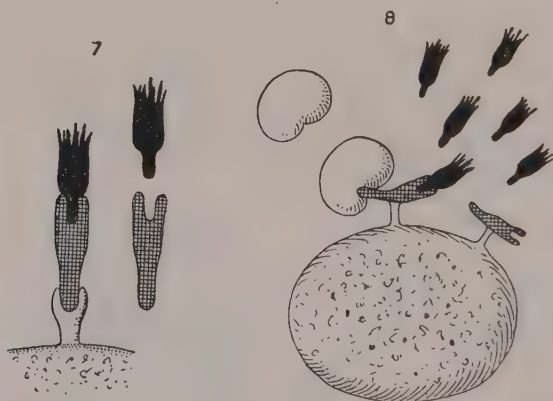


FIG. 464. Diagram to show the relation of Amboceptor and Complement to Red Corpuscles (7) and to the Animal Cell (8). (EHRlich.)

the leucocytes; it is destroyed at a temperature of 60°C . and has been called the *complement*; and (b) a substance which is present in the serum only as a result of the previous injection of some species of red blood corpuscle, which is resistant to the action of heat, and is called the *amboceptor*.

Apparently the amboceptor becomes attached to the red cell first, and then the complement is linked on to this and hæmolysis ensues. Thus, if a rabbit is sensitised against human red cells, and some of its serum taken and heated to 60°C ., it will not now hæmolyse human red cells, because the complement has been destroyed by heat. If the human cells added to it are now removed by centrifugalisation, the addition of complement to them, *e.g.* normal guinea-pig serum, causes immediate hæmolysis, whereas if complement is added to the supernatant serum removed from the red cells, no hæmolysis occurs on adding fresh human cells, because the amboceptor has all been removed by those first added.

The function of the amboceptor thus seems to be to enable the complement already present in normal serum to act upon the red blood corpuscles. We may regard the amboceptor, therefore, as having two haptophore groups, one of which anchors on to the red blood corpuscle, while the other attaches itself to the complement (Fig. 464, 7). The amboceptor *plus* the complement thus comes to resemble the toxin molecule, having a free haptophore group at one end and a toxophore group (the complement) at the other end. The reaction to the injection of the red blood corpuscles consists in the formation of the amboceptor, which is essentially the anti-body of the red blood corpuscle (Fig. 464, 8).

Similar specific anti-bodies, capable of effecting the dissolution of cells or organisms, may be produced by the injection of various species of bacteria, or of animal cells, such as leucocytes, spermatozoa, liver cells, &c., and there can be no doubt that bacteriolytic substances play a considerable part in acquired immunity.

A mixture of red cells and specific hæmolytic amboceptor (heated immune serum) can be used as a test for the presence or absence of complement. If complement is added, hæmolysis occurs, as shown above. Based on this fact, and on the further fact that complement is fixed by the amboceptor in presence of its specific antigen, is the important *complement-fixation test* for the identification of either antigens or amboceptors. An important test related to this is the *Wassermann reaction* for syphilis; the patient's serum (= amboceptors?) is heated to 55° C., mixed with certain lipoids (= antigens?), and then some guinea-pig serum (complement) added. After a time, heated anti-sheep serum from a rabbit, and washed sheep corpuscles, are added, to test whether complement has been fixed or not. Hæmolysis indicates no fixation, and therefore a negative result of the test; absence of hæmolysis, a positive result.

OPSONINS. In some cases the anti-bodies produced by the injection of living on dead micro-organisms do not bring about actual destruction of the bacteria, but alter them in such a way as to make them more susceptible to the action of the phagocytes. If washed white blood corpuscles be mixed with cocci, such as those found in an ordinary boil, they are found to take up the micro-organisms in considerable numbers. The numbers taken up are much increased in the presence of serum derived from an individual who has received repeated vaccine injections of the dead micrococci in question. To the substances in the serum, which thus prepare the micrococci for ingestion by the phagocytes, Wright has given the name of opsonins. The opsonic index of the leucocytes of any individual, in reference to a given species of microbe, is determined by observing the number of the microbes taken up by the leucocytes after treatment with the serum of the individual, and then comparing it with the number taken up by the same leucocytes when the bacteria have been treated with the serum of an average individual.

We thus see that immunity, whether innate or acquired, is extremely complex in character and may depend on one or more of many factors. The immunity of an animal to any given infection may be determined by the absence from his body of receptor groups for the toxin excreted by the microbe responsible for the infection, or by the fact that the receptor groups, though present, are confined to tissues on which the toxophore group can have no influence. Thus, *e.g.*, an attachment of the tetanus toxin to a connective tissue cell would be without effect on the health of the body. Again, immunity may be due to the efficacy of the phagocytes, either of the fluids or of the connective tissues, in ingesting and destroying the micro-organisms, and this, as we have seen, may again be dependent on the presence in, or absence from, the body fluids of substances which, while not destroying the micro-organisms, render them more accessible to the action of the phagocytes. In those cases where the infecting organism secretes a specific toxin, the main line of defence, and the main factor in the production of immunity, is the formation of specific antitoxins to the poison in question. Finally, there may be produced, as a result of the excess of micro-organisms, substances such as the amboceptors, which render the micro-organisms susceptible to destruction by the complements or cytases normally present in the circulating fluids, and possibly themselves derived from the activity or destruction of the leucocytes and other phagocytes of the body.

In this short description we have been able to touch only upon the most salient features of the immunity problem. The question enters strictly into physiology, since, as we have seen, it involves adaptations on the part of the organism to change in itself or its environment.

ANAPHYLAXIS (*v.* also Chapter IV.). If an animal be given injections of a foreign protein, it is found that, a few weeks afterwards, a small dose of the same antigen causes a very severe reaction, or death. This, which appears like the opposite to immunity, is called anaphylaxis. Death occurs owing to profound shock, or, in the guinea-pig, from asphyxia due to constriction of the bronchioles. In any case, generalised contraction of plain muscle is the outstanding feature of anaphylactic shock, and Dale has shown that the plain muscle of a sensitised animal gives a powerful contraction when a trace of the antigen is added, even if the tissue has been previously washed free of all blood. The reaction is, therefore, due to a direct action of the antigen on the tissues, and there is much evidence in favour of the belief that the substances passed out as "precipitins" into the plasma are at a later stage absorbed by the tissue cells, and so sensitise these to the antigen. Thus, the anaphylactic sensibility is found to wax as the precipitin content of the serum wanes.

The close similarity between the anaphylactic responses of different tissues in various species of animals, and the responses of those particular tissues to histamine, led to the suggestion that the phenomena of anaphylaxis were due to the liberation of histamine into the blood, and its subsequent distribution all over the body. The anaphylactic response of isolated tissues discovered by Dale at once negatives this suggestion. Lewis observed that the local anaphylactic response in the human skin was similar to the response to other skin injuries, and it now seems probable that the phenomena are due to the liberation, within the cells, of a histamine-like substance, in consequence of the injury produced by the union of anti-body and antigen.

Anaphylactic shock may be met with in medical practice, as when a second dose of a serum is given after a long interval. The name has also been loosely used to describe many different shock-like conditions, some of which are probably due to a direct toxic action on the vascular system, and in which there are no phenomena of antigenic sensitisation. The anaphylactic reaction is highly specific, and the antigens are invariably proteins.

CHAPTER XXXIX

RESPIRATION

THE MECHANICS OF THE RESPIRATORY MOVEMENTS

In unicellular animals the interchange of gases, *i.e.* the intake of oxygen and the output of carbon dioxide, is carried out by diffusion at the surface of the cell. With increased size of the organism, special organs make their appearance for presenting a large extent of surface to the surrounding medium. In the multicellular animals the actual process of tissue respiration is carried out between the internal medium, lymph, blood, &c., and the individual cells; and the use of the special organ of respiration is to bring the circulating internal medium in intimate relation, over a large area, with the surrounding fluid, whether air or water. In insects we find a large branched system of air tubes, the tracheæ, which are distributed to the finest tissues, renewal of the air in the tubes being provided for by special respiratory movements. In most water animals the respiratory organ is known as the gills, and presents a large surface, well supplied with circulating blood, over which a continual stream of the surrounding water is kept up. In all these animals, therefore, we can distinguish two processes, *viz.* (1) the interchange of gases between the tissue cells and the surrounding lymph, 'internal respiration'; (2) the interchange of gases between the circulating fluid and the external medium, 'external respiration.'

In all air-breathing vertebrates, the organs of external respiration, the lungs, contain numerous air sacs. The renewal of the air in the air sacs is effected by alternate increase and diminution in their size, caused by the movements of respiration, while a rapid circulation of blood is carried out through a fine meshwork of capillaries just underneath the surface of the sacs.

In man the organs of external respiration, the lungs, are built up in the following way: The trachea or windpipe, a wide tube about $4\frac{1}{2}$ inches long, divides below into two main branches—*bronchi*; and these subdivide again and again, becoming gradually smaller. The terminal ramifications or *bronchioles*, which have a strong layer of plain muscle outside the epithelial layer, open, according to Miller (Fig. 465), into *respiratory bronchioles*, and these branch into *alveolar ducts*, which again branch into chambers

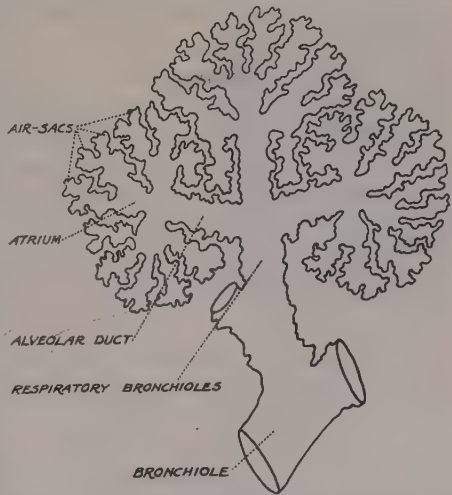


FIG. 465. Diagram of the Air-chambers derived from a Bronchiole. (After MILLER.)

called *atria* ; from each atrium again open out infundibula or *air-sacs*. The walls of all these chambers, respiratory bronchioles, alveolar ducts, atria and air-sacs are covered with minute sacculations called *alveoli* or air-cells, most of which are in the walls of the air-sacs. The larger tubes are kept patent by rings or plates of cartilage in their walls. The smaller tubes have no cartilage, their walls being composed of fibrous and elastic tissue, with a coating of unstriated muscular fibres, which is able by its contraction to occlude the passage. The whole system of tubes is lined with a layer of epithelium—ciliated columnar in the trachea, bronchi, and bronchioles, and cubical over the parts of the respiratory bronchioles not occupied by air cells.

The alveoli are the special respiratory parts of the lung. Their thin walls are composed of connective tissue containing a large number of elastic fibres, and are covered internally by a single layer of extremely thin, large, flattened epithelial cells. The alveoli are closely packed together, so that, in a section of the lung, an alveolus is seen to be in contact with others on all sides. Immediately below the squamous epithelium ramify blood-capillaries derived from the pulmonary artery. These form a close network, and the blood in them is in proximity to air on two sides, being separated from the air in the alveoli only by the thin endothelial cells of the capillary wall and the flattened cells lining the alveoli.

The lungs in their development grow out from the fore part of the alimentary canal into the front part of the body cavity on each side—the pleural cavity. The surrounding body walls become strengthened by the formation of the ribs, so that the lungs are suspended in a bony cage-work, the thorax. Their outer surface is covered with a special membrane, the *pleura*, which is reflected on to the wall of the thorax from the roots of the lungs, and completely lines the cavity in which they lie. The surface of the pleura facing the pleural cavity is lined with a continuous layer of flattened mesothelial cells, and is kept moist by the secretion of lymph into the cavity. Thus, being attached to the thorax only where the bronchi and great vessels enter, the lungs are able to glide easily over the inner surface of the thorax, with which under normal circumstances they are in intimate contact.

RESPIRATORY MOVEMENTS. A constant renewal of the air in the lungs is secured by movements of the thorax, which constitute normal breathing. With inspiration the cavity of the thorax is enlarged, and the lungs swell up to fill the increased space. The capacity of the air passages of the lungs being thus increased, air is sucked in through the trachea. The movement of inspiration is followed by that of expiration, which causes diminution of the capacity of the thorax and expulsion of air. At the end of expiration there is normally a slight pause. The number of respirations in the resting adult is commonly about 17 or 18 a minute. This is, however, much influenced by various conditions of the body, and also by age. Thus, a newborn child breathes about 14 times a minute, a child of five about 26 times, a man of twenty-five about 16, and of fifty about 18. The frequency is increased by any muscular effort, even that of standing. These movements are much affected by psychical activity ; they are to a certain extent under the control of the will, although they can occur in an animal deprived of its brain, and are normally carried out without any special act of volition. We can breathe fast or slow at pleasure, and can even cease breathing for a time. It is impossible, however, to prolong this respiratory standstill for more than a minute ; the need of breathing becomes imperative, and against our will we are forced to breathe.

With every inspiration, the cavity of the thorax is enlarged in all dimensions, from above downwards by the contraction of the diaphragm, and in its transverse diameters by the movements of the ribs.

The diaphragm consists of a central tendon which forms an arched double cupola, to the circumference of which are attached muscle fibres. The diaphragmatic muscles present two main divisions, namely, (1) the spinal or crural part, the fibres of which arise from the upper three or four lumbar vertebræ and from the arcuate ligaments, and are inserted into the posterior margin of the central tendon ; and (2) the sterno-costal part, which

arises by a series of digitations from the cartilages and adjoining bony parts of the lower six ribs and from the back of the ensiform process. These latter fibres pass backwards as they ascend. In the cavity of the larger dome on the right side lies the liver, while the smaller dome on the left side is occupied by the spleen and stomach. These viscera, in the normal condition, are pressed against the under surface of the diaphragm by the elasticity of the abdominal walls. The central part of the diaphragm is thus pressed up into the chest, partly by the intra-abdominal pressure, and partly by the elastic traction of the distended lungs. The upper surface of the central tendon is united to the pericardium. This part, during expiration, is the deepest part of the middle portion of the diaphragm. In expiration, the lateral muscular zone of the diaphragm lies in contact with the lower part of the thoracic wall. During inspiration, the muscle fibres contract and draw the central tendon downwards, so that the lower surface of the lungs descends. The enlargement of the lungs at the lower part of the thorax is aided by the abduction of the floating ribs, produced by the contraction of the *quadratus lumborum* and *deep costal* muscles. In this contraction the diaphragm presses on the contents of the abdomen, so that the abdomen swells up with each inspiratory movement. The middle of the central tendon, where the heart lies, moves less than the two domes, and the part where the vena cava passes through the tendon is practically stationary during normal respiration. In deep inspiration, however, both this part as well as the rest of the pericardial attachment is forcibly depressed towards the abdomen. In quiet breathing, when observed by the Röntgen rays, the mean descent of the right dome in inspiration has been found to be about 12.5 mm., and of the left dome 12 mm. We may say, roughly, that the average descent of the diaphragm during normal respiration is about half an inch. The viscera and the intra-abdominal pressure play an important part in determining the movement of the diaphragm, and especially in preserving the abduction of the lower ribs and so furnishing a fixed point for the muscular fibres of the diaphragm. If the contents of the abdomen are removed from a living animal, the ribs are drawn inwards every time the diaphragm contracts. In children with weak chest walls, and with respiratory obstruction, we may often see a depression round the lower part of the chest, which corresponds to the line at which the diaphragm leaves the chest wall, so that the distending force of the abdominal pressure on the bony walls of the thorax abruptly gives place to the pull of the distended lung. The contraction of the diaphragm may be regarded as a short tetanus.

The enlargement in the other diameters is effected by an elevation of the ribs. Each pair of corresponding ribs, which are articulated behind with the spinal column and in front with the sternum, forms a ring directed obliquely from behind downwards and forwards. With each inspiratory movement the ribs are raised, the obliquity becomes less, and the horizontal distance between sternum and spinal column is therefore increased. Moreover, the ribs from the first to the seventh increase in length from above downwards, so that when they are raised, the sixth rib, for instance, occupies the situation previously taken by the fifth, and the transverse diameters of the thorax at this height become greater. With each inspiration, there is a rotation of the ribs. In the expiratory condition, they are so situated that



Fig. 466. Diagram showing Movements of Diaphragm in Respiration. *i i*, inspiratory position; *e e*, expiratory position. (Yeo.)

their outer surfaces are directed not only outwards but also downwards. As they are raised by the inspiratory movements, they rotate on an axis directed through the fore and hind ends of the rib, so that their outer surfaces are turned directly outwards. In this way a certain enlargement of the thorax cavity is produced. As the thorax is raised, there is always some stretching of the rib cartilages.

In expiration, the processes are reversed, and the cavity of the thorax is diminished in all three dimensions.

The movements of the thorax are effected by means of muscles. Inspiration is performed by the following muscles :

The diaphragm, which is the most important, and almost suffices alone to carry out quiet respiration.

The external intercostal muscles, which raise the ribs.

The serratus posticus superior.

It is probable that an important part is played, even under normal circumstances, in the respiratory movements by the extension of the spinal column. This movement, which is specially marked at the upper part of the thorax, causes an increase in all three diameters of this cavity. The *levator costarum*, which are often included in the inspiratory muscles, are so inserted into the ribs as to be unable to influence their movements. They are concerned, not in respiration, but in lateral movements of the spine.

These muscles are the only ones normally engaged in carrying out inspiration. When, in consequence of muscular exertion or from any other cause, the inspiratory efforts become more forcible, a large number of accessory muscles are brought into play. These are : the scaleni, sterno-mastoid, trapezius, pectoral muscles, rhomboids, and the serratus anticus.

Normal expiration is chiefly effected passively. When the inspiratory muscles cease to contract, the lungs, which were stretched by the previous inspiration, contract by virtue of the elastic tissue they contain, and the thorax itself sinks by its own weight, and by the elastic reaction of the stretched costal cartilages.

It must be remembered, however, that in a position of rest, the elasticity of the thorax is opposed to the elasticity of the lungs. Elasticity of the chest wall would, therefore, tend to produce inspiration. This factor would make inspiration easier at its onset, and would also present an impediment to the carrying out of expiration, so that towards the end of this act there is need for the active co-operation of muscular contractions. It seems possible that more or less muscular activity of the expiratory muscles is alternated with that of the inspiratory muscles. In fact, Sherrington's results on the co-ordination of muscular movements would lead us to assume inhibition of the tone, *e.g.* of the abdominal muscles, during inspiration, and active augmentation of their tone during expiration. Where the tone of the muscle is entirely lost, *e.g.* in the condition of visceroptosis, it has been observed that the diaphragm is thrown out of action, breathing being carried out chiefly by an elevation of the upper part of the thorax. Probably, under normal circumstances, the internal intercostal muscles also contract with each expiration.

Although the action of the intercostal muscles has been a subject of debate and cannot even yet be regarded as definitely settled, physiological experiments serve on the whole to confirm the view first put forward by Hamburger, and based on a consideration of the direction of the fibres. The external intercostals pass from one rib to the next below, downwards and forwards. Hence, if a pair of ribs be isolated from the rest of the chest wall, leaving the vertebral and costal attachments intact, contraction of these muscles will cause a rise of both ribs. This result will be evident from a considera-

tion of Fig. 467, where ab is a fibre of the external intercostal muscles, passing from the rib vs to be attached to the rib $v's'$ at b . When ab contracts, the tension it exerts on its two attachments can be resolved into two components ac acting downwards and bd acting upwards. bd , however, acts at the end of the long lever bv' , whereas ac acts at the end of the short lever av . Hence the raising effect will overcome the depressing effect, and both ribs will rise.

The fibres of the internal intercostals run in the opposite direction to the external muscles, and from a consideration of Fig. 468 it is evident that their effect will be to depress any pair of ribs, thus acting as expiratory muscles.

Owing to the fact that the costal cartilages make an angle with the bony ribs, the fibres of prolongation of the internal intercostals, *musculi intercartilaginei*, have the same relation to their attachments that the external intercostals have to the bony ribs. Their action, therefore, must be to raise the cartilages and flatten out the angle between the cartilaginous and bony ribs, so that they must act with the external intercostals as inspiratory muscles.

In forced expiration, a large number of muscles may take part—such as the serratus posticus inferior and the muscles forming the wall of the abdomen, *i.e.* the rectus, obliquus, and transversus abdominis muscles.

As the lungs are distended with each inspiration, their position changes in relation to the thoracic wall. All parts are not equally distensible in the normal position of the lungs. There are three areas which are in contact with the nearly stationary parts of the thoracic wall and cannot therefore

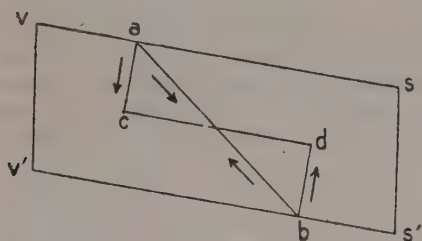


FIG. 467.

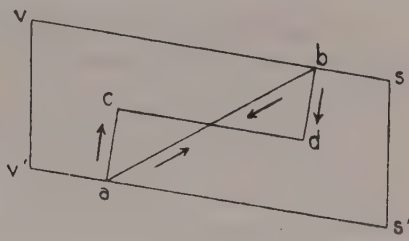


FIG. 468.

be directly expanded. These are (1) the mediastinal surface in contact with the pericardium and structures of the mediastinum; (2) the dorsal surface in contact with the spinal column and with the spinal segments of the ribs; (3) the apical surface lying in contact with the deep cervical fascia at the root of the neck. The expansion of these portions of the lung is in a downward direction and is indirectly caused by the movement of the diaphragm. The roots of the lungs move, with inspiration, slightly forwards and downwards. With the expansion of the lungs at inspiration there is also an increase in length and width of all the air-tubes, even of the trachea and large bronchi, but especially of the smaller ones. The actual alveoli are probably little, if at all, stretched at inspiration, but merely become flatter and wider. At expiration, all these changes are reversed.

The extent and boundaries of the lungs can be easily ascertained in the living subject by means of *percussion*. On tapping the finger laid on the chest, a sound is emitted, which varies with the nature of the subjacent tissues. If this is lung tissue filled with air, a clear resonant tone is obtained; where it is solid tissue, such as the heart, or a lung consolidated with inflammatory products, or the liver, a dull sound is obtained. It is easy to show that the resonant area of the chest increases with each inspiration. The apices of the lungs extend about one inch above the clavicle anteriorly, and reach as high as the seventh spinous process behind. During moderate expiration the lower margin of the lungs extends, in front, from the upper border of the sixth rib at its insertion to the sternum, and runs obliquely downwards to the level of the tenth rib at the back of the chest. During the deepest inspiration the lungs descend, in front, to the seventh intercostal space, and behind, to the eleventh rib, while during deepest possible

expiration, the lower margins of the lungs are elevated almost as much as they descend during inspiration. In the front of the chest a triangular space can always be marked out over the heart, where the note obtained on percussion is dull. This space is bounded on the right by the left border of the sternum, and extends out as far as the cardiac apex, being bounded above by the fourth costo-sternal articulation and below by the sixth costal cartilage.

BREATH SOUNDS. If the ear be applied to the chest wall, either directly or through the medium of a stethoscope, each inspiration is found to be accompanied by a fine rustling sound, the 'vesicular murmur.' It is thought to be caused by the sudden dilatation of the air vesicles during inspiration, or perhaps by the current of air passing from the narrow terminal bronchioles into the wider infundibula. It is important to remember that this sound is heard only during inspiration, and over healthy lungs. On listening over the larger air passages, *i.e.* the larynx, trachea, and bronchi, we hear a much louder sound which accompanies both expiration and inspiration, and may be compared to a sharp whispered *hah*. This is known as the 'bronchial murmur.' It can be heard also at the back of the chest between the scapulæ at the level of the fourth dorsal vertebra, where the trachea bifurcates. In all other parts of the chest the healthy lung prevents the propagation of this sound to the chest wall. If, however, the lung is solid, as occurs in pneumonia, it conducts the sound easily from the large air tubes to the chest wall. Bronchial breathing at any part of the chest, other than that immediately over the air tubes, is therefore a distinctive sign of consolidation of the lung. Absence of breath sounds at any part of the chest implies, either that air is not entering that part of the lung, or that the lung is separated from the chest wall, *e.g.* by effused fluid.

INTRATHORACIC PRESSURE. Even at the end of expiration the lungs are in a stretched condition. This is shown by the fact that if, in an animal or in the corpse, an opening be made into the pleural cavity, air rushes into the opening and the lungs collapse, driving a certain amount of air out through the trachea. Since the lungs are always tending to collapse, it is evident that they must exert a pull on the thoracic wall. This pull of the lungs gives rise to a *negative pressure* in the pleural cavity. If we connect a mercurial manometer with the pleural cavity, we find that the pull of the lungs amounts, in the corpse, to 6 mm. of mercury. If the lungs are fully distended, as after full inspiration, the elastic forces are brought more into play, and the negative pressure in the pleura may amount to 30 mm. Since the lungs are always tending to collapse, respiration becomes impossible directly free openings are made into the pleural cavities on both sides. With each inspiratory movement, air rushes in through these openings, so that the thoracic movements can no longer exert any influence on the volume of the lungs. The negative pressure in the thorax is diminished by any factor decreasing the elasticity of the lung tissue. Thus, in an old man, where the elastic tissue is degenerated and the alveoli are enlarged, giving rise to the condition known as *emphysema*, the lungs may collapse only slightly, or not at all, on opening the chest. The lungs do not collapse on making an opening in the chest of a new-born mammal; but this is owing to the fact that they completely fill the thorax in the expiratory position, and it is only later that, with the growth of the ribs, the thorax gets, so to speak, too large for the lungs, which are therefore stretched to fill it.

The force exerted by the inspiratory muscles is nearly all spent in overcoming the elastic resistance of the lungs and costal cartilages. A free access of air is provided for by contractions of certain accessory muscles of respiration. With each inspiration the glottis is widened by abduction of the vocal cords. When the glottis is observed by means of the laryngoscope, a rhythmical separation and approximation of the vocal cords are observed, synchronous respectively with inspiration and expiration (Fig. 197, p. 351). When inspiration is laboured, the *alæ nasi* are dilated by the action of the *dilator nasi*. This movement of the nostril, which is constant in many

animals, becomes very marked in children suffering from any respiratory trouble.

If a manometer be connected with one of the nostrils, so as to register the pressure in the air cavities, it is found that there is a negative pressure of -1 mm. Hg with inspiration, and a positive pressure of 2 or 3 mm. with expiration. With forced inspiration, the negative pressure may amount to -57 mm. Hg, and with forced expiration there may be a positive pressure of $+87$ mm.

PULMONARY VENTILATION. Under no circumstances can we by forced expiration empty the lungs of air. At the end of the most forcible expiration, if the pleura were perforated, the lungs would collapse and drive more air through the trachea. When breathing quietly, a man takes in and gives out at each breath about 500 c.c. of air, measured dry and at 0° C. If measured moist and at the temperature of the body, viz. 37° C., the volume would be about 600 c.c. This amount is known as the *tidal air*. By means of a forcible inspiratory effort, it is possible to take in about 1500 c.c. more (*complemental air*). At the end of a normal expiration a forcible contraction of the expiratory muscles will drive out about 1500 c.c. more (*supplemental air*). These three amounts together constitute the 'vital capacity' of an individual. This total may be determined by means of the spirometer, a small gasometer with a gauge by which the amount of air in it can be at once read off. The person to be tested fills his lungs as full as possible, and then expires to the utmost into the spirometer. The vital capacity is greatest when standing, and least when lying in the prone position, the difference being about 500 to 750 c.c. Individual variations are great. The air left in the lungs after the most vigorous expiration is known as the *residual air*.

The residual air may be determined by letting a person expire to the utmost extent, and then connecting with his mouth or nose a bag of known capacity filled with hydrogen. The subject of the experiment then inspires and expires into the bag two or three times, ending in the same state of forced expiration as he began. The volume and hydrogen content of the gas in the bag is now determined. Supposing, for example, the bag held 4000 c.c. hydrogen, that after two respirations the total volume is unaltered, but the gas is then found to consist of 3000 c.c. hydrogen and 1000 c.c. pulmonary gases. Since the gas in the lungs must have the same composition, and since 1000 c.c. hydrogen have disappeared from the bag, it is evident that the lungs will contain 1000 c.c. hydrogen and $\frac{1000}{0.3}$, i.e. 330 c.c. pulmonary gases. Thus, the total volume of gas left in the lungs at the end of the forced expiration was 1330 c.c., which is the residual volume for the individual.

As a result of actual determinations, we may assume the residual air in the lungs as something between 600 and 1200 c.c.

Of the 500 c.c. of tidal air taken in at each inspiration, only a certain part reaches the alveoli, part being required to fill the air tubes, trachea, bronchi, and bronchioles which lead to the air cells. The volume of these air tubes is called the '*dead space*,' and is normally taken as about 140 c.c., so that, of the 500 c.c., about 360 c.c. actually reach the alveoli. For the same reason, the expired air represents the air from the alveoli (360 c.c.), diluted with 140 c.c. of dead space air which has remained in the air tubes and undergone very little change, other than the elevation of temperature and saturation with aqueous vapour. There is no doubt, however, that it is incorrect to regard the volume of the dead space as constant, since not only do the branches of the bronchial tree show at inspiration an increase, and at expiration a decrease, in all dimensions, but the volume of the physiological dead space no doubt varies with alterations in the state of the bronchial musculature and various other factors. It is, for instance, claimed to be increased in exercise.

THE BRONCHIAL MUSCULATURE

All the air tubes have a middle layer of circular or oblique plain muscle fibres, which in the bronchioles is thick and complete. Contraction of these has the following effects: (1) a constriction of the bronchi and bronchioles; (2) a diminution of the air space of the lungs, and therefore of the volume of the lung; (3) an increased resistance to the passage of the air into, and out of, the alveoli. Changes in the condition of contraction of these muscle fibres may be studied in two ways. In the first method, artificial respiration is carried out, a constant volume of air being blown in and sucked out at each respiration. Any diminution in the calibre of the bronchioles must increase the resistance to the incoming current of air, and so cause a rise of pressure in the tracheal tube. By the second method, artificial respiration at a constant pressure is made use of. Any changes in the bronchioles will in this case

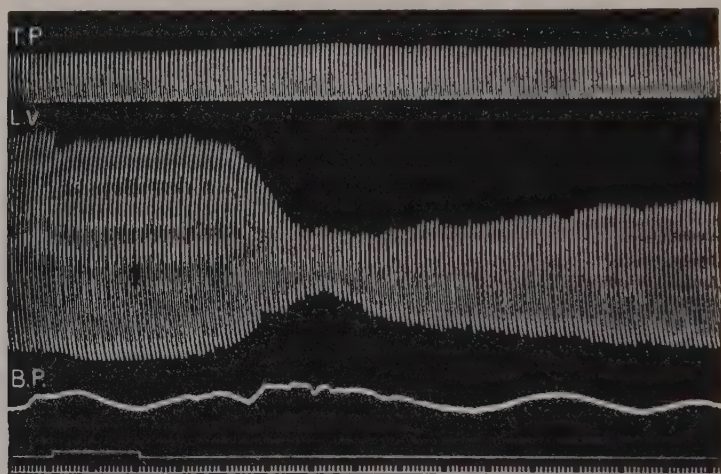


Fig. 469. Tracings of the Volume Changes of the Lung, with constant Variations of Tracheal Pressure. (BRODIE and DIXON.)

T.P. tracheal pressure. L.V. lung volume. B.P. blood pressure (Zero B.P. 17 mm. below time marker). Showing constriction of bronchial musculature as a result of vagus excitation.

affect the *volume* of air entering the lungs at each stroke of the pump, and this can be measured by recording either the passive respiratory movements of the chest or the changes in volume of a lobe of the lung enclosed in a plethysmograph (Brodie and Dixon) (Fig. 469). By both these methods it has been shown that stimulation of the peripheral end of either vagus causes constriction of the bronchioles. As a rule, there is little tonic action of the vagi, section of both vagi leaving the respiratory pressure curve almost or quite unaltered. It is very easy to bring about a vagus tonus by allowing the animal to inhale air containing 3 to 4 per cent. carbon dioxide. A peripheral tonus may also be produced by administration of muscarine or pilocarpine. In the latter case, Brodie and Dixon have shown that stimulation of the vagus may cause relaxation of the bronchioles. This double effect of the same nerve, according to the state of contraction of the muscle, is often seen with plain muscle (*q.v.*). There are, however, definite inhibitory nerve fibres to the bronchioles, which are almost certainly of sympathetic origin, and full relaxation of the bronchial musculature is obtained by the administration of adrenaline.

According to some investigators, there may also be afferent fibres from the bronchial muscles, by which reflex adjustment of their degree of contraction may be effected, and it has also been claimed in this connection that rhythmic contraction of the bronchial muscle happens at each expiration. Also, peristaltic movements of the bronchial muscle have been described as occurring when the passages become blocked.

THE EFFECTS OF BRONCHIAL CONSTRICTION : ASTHMA.

Under the influence of vagal stimulation or of carbon dioxide, the pressure necessary to drive the normal amount of air into the lungs at the same rate may be raised in the dog from 125 to 300 mm. H_2O . We should therefore expect that, in cases where bronchial constriction is present, there would be difficulty both in inspiration and expiration. There is, however, a difference in the mechanical conditions of the bronchi during the two phases of a respiratory movement. Normally, especially in inspiration, the elastic

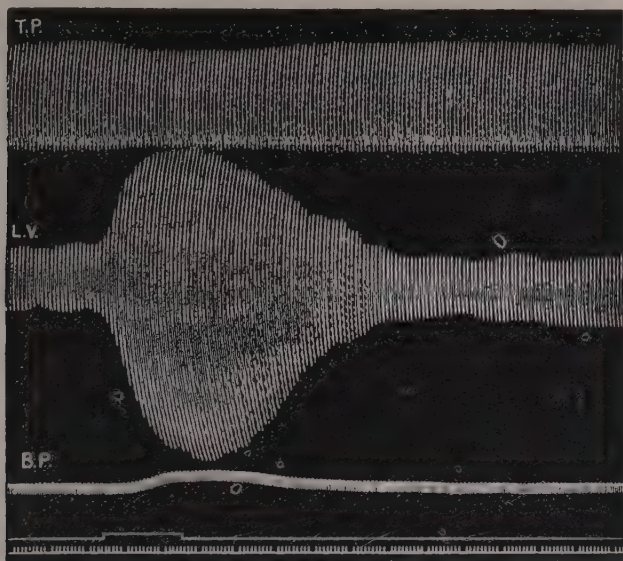


FIG. 470. Tracing showing Inhibitory Effect of Vagus on the Bronchial Tonus produced by 0.01 gramme Pilocarpine. Lettering as in Fig. 469.

structure of the lungs is drawing upon the bronchial wall, tending to maintain it patent, and so opposing even a powerful action of the bronchial muscle. In expiration, the pull of the lung tissue on the bronchial wall, though still present, is much lessened. If, however, the expiratory muscles contract vigorously, the intrapleural pressure becomes positive, and the pull of the lung tissue on the bronchial walls is changed into a pressure tending to obliterate their lumen and so impede the outflow of air.

It is evident, therefore, that in the presence of a spasmodic contraction of the bronchial muscles, inspiration, especially if forced, will be easy enough, but expiration difficult, and more so if forced. Hence, expiration must be left to the elastic reaction of the lungs and becomes slow and prolonged. Moreover, it will be of advantage not to depart too much from the inspiratory position, which, by reinforcing the elastic forces, keeps the bronchial tubes patent. We thus get the typical breathing which occurs in man in cases of spasm of the bronchial muscles, known as *asthma nervosum*. This type of breathing is often described as being marked by *expiratory dyspnœa*, though

actually it is the inspiratory muscles which, in these cases, are contracted to their uttermost; the expiratory muscles, such as the abdominal, will be found to be quite flaccid even during expiration.

THE CHEMISTRY OF RESPIRATION

EXPIRED AIR. As a result of the continual oxidative processes associated with their life and activity, the tissues of a man of 70 kg. body weight consume, on an average during working hours, about 400 c.c. oxygen per minute. This oxygen is used for the oxidation of the various materials which are subjected to combustion in the body, of which the element carbon is a principal constituent. The tissues, in consequence, produce large quantities of carbon dioxide. The oxygen required by the tissues is taken from the blood, and the carbon dioxide formed is, in return, passed out into the blood. Hence, the venous blood is partially deprived of the oxygen which was present in the arterial blood, but it contains more carbon dioxide. In its passage through the lungs, the blood is again arterialised, oxygen passing into it and CO_2 out, owing to an exchange with the air in the air-sacs. This air is continually renewed by breathing, and we therefore find that the expired air contains less oxygen, and more carbon dioxide, than that which is inspired.

When the expired air of normal resting persons at sea-level is collected (*e.g.* by the use of valves and a Douglas bag, as described in Chapter XXVIII.) it is found on analysis to present the following average comparison with inspired air:

	INSPIRED AIR		EXPIRED AIR
Oxygen	20.96 vols. per cent. ...		16.4 vols. per cent.
Nitrogen (including argon)	79.00 " " ...		79.5 " "
Carbon dioxide	0.04 " " ...		4.1 " "

These figures for the composition of inspired and expired air refer to dry air, at a temperature of 0°C. , and a pressure of 760 mm. Under normal circumstances, inspired air contains a variable amount of aqueous vapour and has a variable temperature. Expired air is fully saturated with aqueous vapour and has the temperature of the body, 37°C. The tension of aqueous vapour at this temperature amounts to 50 mm. Hg. Thus when a man is breathing dry air at a pressure of 760 mm. Hg, the pressure of the mixture of permanent gases in the alveoli of his lungs will be only $760 - 50$, *i.e.* 710 mm. Hg.

Calculation from these data shows that, whereas about 400 c.c. of oxygen are used up per minute by a normal resting man, only about 340 c.c. of carbon dioxide are added to the expired air in the same time, while the total volume of nitrogen leaving the lungs is the same as that taken in. In the analysis, the nitrogen *percentage* is seen to be higher in the expired air. This is because the volume of air expired is less than that inspired, owing to the disappearance of a certain amount of oxygen, without the production of a corresponding amount of carbon dioxide, so that the *relative* amount of nitrogen is slightly increased. The reason for this disappearance of oxygen is that when fats and proteins are being consumed, some of it is used for the combustion of hydrogen and for the partial oxidation of nitrogen, as well as in burning carbon. As explained in Chapter XXVII., the ratio of the volumes $\frac{\text{CO}_2}{\text{O}_2}$ which are exchanged in a given time, and which is called the respiratory quotient, is normally about 0.85, but varies according to the nature of the materials subjected to combustion in the body.

ALVEOLAR AIR. As already explained, only about 360 c.c. of the 500 c.c. of air drawn in at an average breath reach the alveoli, about 140 c.c. being required to fill the dead space. Hence, the alveolar air must contain more

carbon dioxide and less oxygen than the mixed expired air, which consists of alveolar air *plus* unchanged dead space air which is expelled first on expiration.

At the end of an expiration, the dead space has been swept out by, and remains filled with, alveolar air. Based on this fact, a sample of alveolar air may be obtained for analysis in the following way (Haldane). A piece of india-rubber tubing is taken, of about 1 inch diameter and 4 feet long. Into one end (Fig. 471) is fitted a mouthpiece, the other being left open. About 2 inches from the mouthpiece is fixed a gas sampling-bulb, which is provided with three-way taps at the upper and lower ends. Before an experiment the bulb is filled with mercury, and the lower tap left open, or else the bulb is completely exhausted. The subject of the experiment, after breathing *normally* a few times, at the end of a normal inspiration puts his mouth to the tube, expires quickly and deeply, and closes the mouthpiece with his tongue. The tap of the sampling-bulb is then turned, and the air last expelled from the lungs (which is therefore pure alveolar air) rushes into the bulb. The tap of the bulb is then turned off, and the gas may be removed for analysis. A similar sample is then taken, in which the subject expires deeply at the end of a normal expiration. This sample will, of course, contain more CO_2 and less O_2 than that obtained at the end of inspiration. The mean of the two samples is taken as the average composition of the subject's alveolar air.

The difference between the composition of expired air and alveolar air is determined by the dilution of the alveolar air with that contained in the dead space. Hence, with shallow breathing there will be a large difference, but this will decrease with increased depth of respiration. Thus, if the alveolar air contained 6 per cent. CO_2 and the dead space amounted to 150 c.c., the expired air would contain only 3 per cent. CO_2 when the person was taking in only 300 c.c. at each respiration. If, however, he was breathing slowly and deeply, so as to raise the tidal air to 1500 c.c., only one-tenth of this would be represented by the dead space, and the expired air would contain nine-tenths as much CO_2 as the alveolar air, *i.e.* 5.4 per cent.

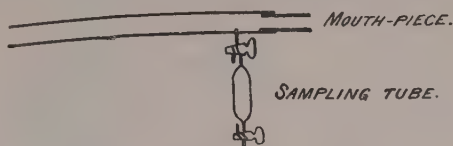


FIG. 471.

The changes in the composition of alveolar air with respiration are by no means so marked as those produced in the tidal air, since the latter forms only a small proportion of the total air in the lung alveoli. Thus, at the end of a normal expiration, the alveoli still contain 2500 c.c. of gases. In inspiration 360 c.c. atmospheric air are taken into this space and mixed with the 2500 c.c. already there. The 'ventilation coefficient' in quiet breathing is therefore only one-seventh, and the change in the oxygen and carbon dioxide content of the alveolar air produced by this access of 360 c.c., will amount to less than one-half per cent. This is illustrated by the following figures from Haldane, giving the alveolar content in carbon dioxide at the end of inspiration and at the end of expiration respectively.

ALVEOLAR CO_2 PER CENT.

Individual	Alveolar CO_2 at end of inspiration. (Mean of twelve observations)	CO_2 at end of expiration	Mean
J. S. H.	5.54	5.70	5.62
J. G. P.	6.17	6.39	6.28

We can thus speak of an average composition of alveolar air, which, in spite of the constant ventilation, differs from the external air in containing an excess of carbon dioxide and a deficit of oxygen.

THE BLOOD GASES. It was shown by Magnus, in 1837, that the blood passing to the lungs contained more carbon dioxide and less oxygen than that passing away from the lungs. The effects of this discovery were to show

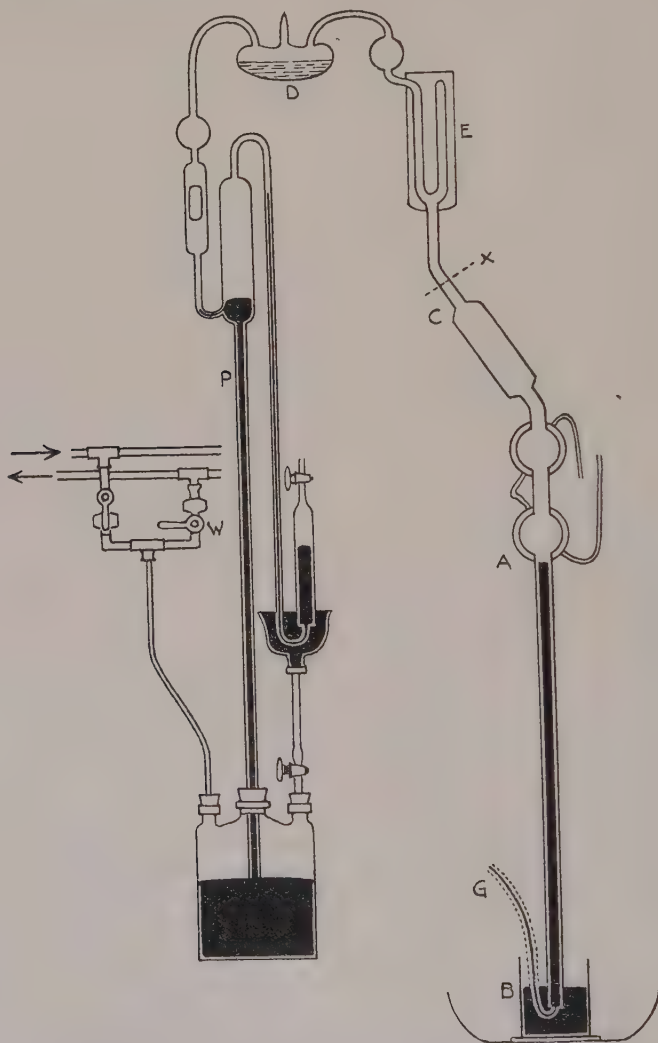


FIG. 472. Buckmaster and Gardner's Tapless Blood-gas Pump.
(Modified from *Journal of Physiology*.)

that combustion does not occur in the lungs, as Lavoisier had suggested, but that the blood acts simply as a carrier of the oxygen from the lungs to the tissues, and of the carbon dioxide from the tissues to the lungs. We thus learnt to distinguish between external and internal respiratory processes. If any further proof is required that it is the tissues themselves which utilise oxygen and produce carbon dioxide, we may refer to the fact that any surviving tissue, quite free from blood, can be shown to absorb gaseous oxygen

and give out carbon dioxide. A consideration of the chemical mechanisms involved in the process of external respiration necessitates an investigation of the manner in which gases are held by the blood and of the factors which are responsible for the transfer of oxygen and carbon dioxide from alveolar air to blood, and from blood to alveolar air.

If blood be exposed to a Torricellian vacuum at the ordinary temperature, the whole of its contained gases is given off. For the purpose of extracting the blood gases, a great variety of pumps have been devised. In every case, a glass vessel is evacuated by means of the mercury pump, and is then put into connection with a reservoir containing blood which has been defibrinated, or has been prevented from clotting by the addition of oxalate or citrate. In all these pumps the main difficulty which arises is the exclusion of atmospheric air, and it is therefore important to dispense so far as possible with taps. One of the best modifications of the Töpler mercury pump is that employed by Buckmaster and Gardner (Fig. 472), which differs from the pump devised by Bohr chiefly by the absence of taps.

The construction of the pump is shown in the diagram. The actual pump consists of the part P. The bulb is prolonged below by a wide tube dipping into the mercury in the Woulfe bottle. The upper part of the bottle is filled with water and connected by two taps at w with the water-supply and with a sink. The water being turned on, mercury is forced up into P; as it rises, it carries before it a glass valve which prevents its further passage, so that it can escape only by the narrow tube, driving before it all the air previously contained in P. The water-supply is now turned off, and the tap to the sink turned on. The mercury runs back. Air cannot enter, and the valve therefore sinks and allows the air in the blood receiver A and the rest of the apparatus to escape into P. The process is repeated many times, until a high vacuum is produced in the whole apparatus. A measured quantity of blood is now introduced, through G, and at once rises into the lower bulb A. This is surrounded by a condenser jacket, through which warm water is passed, and E is another condenser containing ice. The blood boils in the vacuum, and the gases escape into P, and may be driven off and collected over mercury by raising the mercury in P. The process of exhaustion is repeated until no more bubbles rise into the collecting tube on filling the bulb P with mercury. D is a sulphuric acid chamber for drying the gases as they pass from the blood to the bulb P.

By the use of the pump, about 60 c.c. of mixed gases may be obtained from 100 c.c. of blood; this consists of oxygen, carbon dioxide, nitrogen, and argon. Argon is present only in insignificant quantities, about 0.04 volume per cent. The nitrogen also forms only between one and two volumes per cent. and is present in the same proportion in both arterial and venous blood. The amounts of oxygen and carbon dioxide in these two kinds of blood differ, however, within wide limits. The following Table represents the average composition of the gases obtained from an artery and a vein of a dog:

From 100 vols.		May be obtained		
		Of oxygen	Of carbon dioxide	Of nitrogen
Of arterial blood . . .	20 vols.	40 vols.	1 to 2 vols.	
Of venous blood . . .	8 to 12 vols.	46 "	" "	"
Measured at 760 mm. and 0° C.				

The use of vacuum pumps, though a standard method, is very laborious, and since it demands relatively large amounts of blood is not widely applicable.

The principle introduced by Haldane (*vide* p. 688) for the determination, by the use of ferri-cyanide, of the oxygen combined in the form of oxyhæmoglobin, may be successfully applied to small quantities of blood, such as 1 c.c., and in the same sample of blood the carbon dioxide may also be determined. In this way it becomes practicable to make analyses of a patient's blood, or experiments on small organs where it is desired to determine their gaseous metabolism by comparing the arterial with the venous blood.

The apparatus devised by Haldane (*vide* p. 688) may be used for this purpose, using 2 c.c. of blood.

Barcroft's apparatus for dealing with 1 c.c. of blood is shown in Fig. 473. The apparatus consists of two bottles of identical size (about 30 c.c.) attached to a manometer, the tubing of which is 1 mm. bore. The manometer is filled with clove oil. The constant of the apparatus must be determined; this depends on the capacity of the bottles with their connections. This is done by finding what rise of pressure in the apparatus is produced by the addition of a known volume of air to one bottle, the other bottle being in connection only with the manometer. The constant $K = \frac{V}{P}$; thus if adding 150 c.mm. of air to the bottle raises the pressure by 50 mm. (difference of level in manometer), the constant is $\frac{150}{50} = 3$; i.e., when gas is liberated, each millimetre difference of pressure in the manometer corresponds to 3 c.mm. of gas added to that

bottle; the same holds good if gas is absorbed in the bottle, with production of reduced pressure. Both taps must be closed during use.

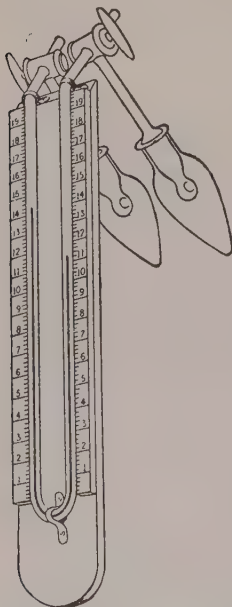


FIG. 473. Barcroft's Blood Gas Apparatus.

To Determine the Oxygen Capacity of a Sample of Blood. Place in each bottle 2 c.c. of ammonia (4 c.c. strong ammonia per litre) and 1 c.c. of blood. Add a few milligrammes of saponin. Whisk the bottles round until the blood is thoroughly laked and oxygenated. Rub tap-grease on the stoppers. Put 0.2 c.c. of a fresh saturated solution of potassium ferricyanide in the small reservoir in the stopper of one bottle. Place both bottles on their stoppers, and hang the apparatus over the side of a water bath, with the bottles immersed and with both taps open. Close the taps, after five minutes, and note whether the manometer remains stationary. When this is so, read the level of the oil and tilt the apparatus, so that the ferricyanide runs into the laked blood. Shake thoroughly, replace in the bath, and repeat this several times till a constant difference of level is obtained. Let this difference of level be y mm., x the volume of oxygen given off in cubic millimetres, and K the constant of the apparatus: then $x = y \times K$. This result must be reduced to dry volume at N.T.P. If desired, the operation can be repeated, using the other bottle.

To Determine the Oxygen Content of a given Blood. If we wish to determine the actual amount of oxygen present as oxyhæmoglobin in the sample, the blood must be carefully introduced in one bottle, so as to lie below the ammonia and not to come in contact with the air. Into the reservoir of that bottle 0.2 c.c. of ferricyanide is placed. In the other bottle is similarly placed 1 c.c. of fully oxygenated blood, but no ferricyanide. The bottles are placed on their stoppers as before, and the apparatus immersed in the bath, with both taps open until it has attained a constant temperature. The taps are then closed and the height of the column of oil noted. The blood is then laked by rotating the apparatus, and after allowing five minutes for complete laking, the ferricyanide is tipped in. The rest of the determination is carried out as above.

To Determine the Percentage Oxygen Saturation of a given Blood. Proceed as above, up to the point of laking both the saturated and unsaturated bloods. Replace in water bath until the temperature is equal, and read off the manometer. This reading (A) represents the amount of oxygen absorbed to complete the saturation of the sample. Now open both taps, restore the level, close the taps again, tip in the ferricyanide, shake out the oxygen, and so determine the oxygen capacity, as a reading of (C) mm.

The percentage saturation:
$$S = \frac{\text{content}}{\text{capacity}} \times 100,$$

and since the content (B) = capacity (C) — Deficit (A)

$$\begin{aligned} \therefore S &= 100 \frac{B}{C} \\ &= 100 \frac{(C-A)}{C}. \end{aligned}$$

The same apparatus may be used as a *differential blood-gas manometer*, by which it is possible to compare the oxygen contents of two samples of blood, *e.g.* of arterial and venous blood. For this purpose 1 c.c. of the arterial blood is introduced into one bottle and 1 c.c. of the venous blood into the other bottle, in each case under 2 c.c. of weak ammonia. The bottles are then placed on the apparatus and immersed in the water bath until no change occurs in the height of the column of oil. The two taps are then closed and the apparatus is vigorously shaken. The blood on each side is laked and, in contact with the air in the bottles, becomes completely saturated with oxygen. If the two bloods contain the same amount of reduced hæmoglobin, no difference will be produced in the level of the oil in the two tubes. If, however, one be arterial and the other venous, the venous blood will absorb more oxygen from its bottle than the arterial blood from its side of the apparatus, so that the oil will rise in the tube on the side of the venous blood. From the degree of rise, the difference in the amount of oxygen taken up by the blood on the two sides can be reckoned, and this figure will express the relative saturation of the hæmoglobin in the two samples of blood.

The carbon dioxide may be determined in the same sample of blood by adding lactic acid in the same way as potassium ferrieyanide was previously added.

The condition of a gas in the blood can be judged by the amount of gas which the blood will take up when exposed to different pressures of the gas. If a gas is in simple solution, the amount of it dissolved varies directly with its partial pressure. When only one gas is present, the whole pressure is due to that one gas. Thus, if water takes up a certain bulk of a gas at a given temperature and pressure, it will take up twice as much if the pressure of the gas be doubled. The absorption coefficient of a liquid for a gas at a given temperature is expressed by the number of cubic centimetres of gas, measured at normal temperature and pressure (0° and 760 mm. Hg), which will be taken up at the particular temperature by 1 c.c. of the liquid when the gas is at a pressure of 760 mm. Hg. The absorption coefficient diminishes with rise of temperature. The following Table represents the absorption coefficients for some important gases in water at various temperatures between 0° and 40° C. :

Temperature	Oxygen	Carbon dioxide	Carbon monoxide	Nitrogen
0	0.0489	1.713	0.0354	0.0239
10	0.0380	1.194	0.0282	0.0196
20	0.0310	0.878	0.0232	0.0164
30	0.0262	0.665	0.0200	0.0138
40	0.0231	0.530	0.0178	0.0118

From this Table we see that 100 c.c. of water at 0° C. will absorb 4.89 c.c. oxygen at one atmosphere. If the pressure be raised to two atmospheres, the volume of gas absorbed, when measured at N.T.P., will be 9.78 volumes. If, therefore, we plot out the absorption of the gas on a curve, of which the ordinates represent the amount of gas dissolved, and the abscissæ the different pressures of the gas, we shall get a straight line. The amount absorbed depends on the partial pressure of the particular gas considered, and is not altered by the presence of other gases at the same time. The normal pressure of the whole atmosphere is 760 mm. Since the atmosphere consists roughly of four parts of nitrogen with one part of oxygen, the atmospheric pressure is due, as to one-fifth to the oxygen, and as to four-fifths to the nitrogen. If we shake up water at 0° C. with the atmospheric air at the ordinary pressure, 100 c.c. of water will absorb 4.89 c.c. $\times \frac{1}{5}$ of oxygen, and of nitrogen $2.39 \text{ c.c.} \times \frac{4}{5}$. We may therefore extend our statement as to the solubility of gases in liquids, and say that *the amount of gas dissolved in a liquid is proportional to the partial pressure of the gas.*

When water is shaken up with a gas until it will take up no more, *i.e.* until it is saturated for that pressure, a state of equilibrium exists between the gas dissolved in the fluid and the gas in contact with the fluid. In this state of equilibrium, the number of molecules of the gas entering the fluid in unit time is exactly equal to the number of molecules of the gas leaving the fluid. If we remove the liquid after saturation, say, at one atmosphere, to a vessel where it is in contact with the same gas at a pressure of half an atmosphere, the liquid will give off gas until the amount left in solution is diminished to one-half. The gas dissolved in a liquid thus has a pressure or *tension* which tends to make it escape from the liquid. The only way in which we can measure this tension is by finding what pressure of the gas is in exact equilibrium with the liquid. Thus, if we take some water containing carbon dioxide in solution, divide it into two parts, and shake up one part with a gaseous mixture containing 4 per cent. of carbon dioxide and the other part with a mixture containing 5 per cent. of carbon dioxide, and find that the solution loses gas to the former and takes up carbon dioxide from the latter, we may conclude that the tension of carbon dioxide in the original fluid was something between 4 and 5 per cent. of an atmosphere. It is by some such means that the tensions of gases in the blood are measured, the instruments for this purpose receiving the name of *aerotonometers*.

The solvent power of water for gases is diminished if the water contains other solid substances in solution. Blood plasma, or blood corpuscles, will therefore have a smaller solvent power for gases than has pure water. It has been shown by Bohr that the depression of solubility caused by the presence of proteins or salts in solution is similar for all gases. The absorption coefficient of blood plasma for gases is reduced to 97·5 per cent. of that for pure water, and of blood to 92 per cent., that of the blood corpuscles being as low as 81 per cent. We may thus reckon the absorption coefficient of blood plasma, blood and blood corpuscles for oxygen, nitrogen and carbon dioxide.

	Oxygen		Nitrogen		Carbon dioxide	
	15°	38°	15°	38°	15°	38°
Blood plasma .	0·033	0·023	0·017	0·012	0·994	0·541*
Blood .	0·031	0·022	0·016	0·011	0·937	0·511
Blood corpuscles .	0·025	0·019	0·014	0·010	0·825	0·450

THE CARRIAGE OF OXYGEN BY THE BLOOD. From the above Table we see that 100 volumes of blood at 38° C. might contain 2·2 c.c. of oxygen in solution, if the blood had been exposed to oxygen at a pressure of one atmosphere. The blood in the lungs is, however, exposed to air which contains only about one-sixth of its volume of oxygen, so that the total amount of oxygen present in solution in arterial blood cannot be more than one-sixth of 2·2, *i.e.* about 0·36 c.c. per cent. Since arterial blood, or blood saturated with oxygen by shaking with air, will yield nearly twenty volumes per cent. of oxygen to a Torricellian vacuum, the oxygen cannot be in simple solution, but must be in some form of combination with some of the constituents of the blood. Of this oxygen, practically the whole is contained in the red blood corpuscles, in combination with hæmoglobin, the plasma containing no more than can be accounted for by simple solution.

* Van Slyke and his collaborators have estimated the solubility co-efficient of CO₂ in blood plasma at 38° C. as 0·510 instead of 0·541 as given by Bohr.

One gramme of hæmoglobin can absorb 1.34 c.c. of oxygen. If a solution of oxyhæmoglobin be subjected in an air-pump to gradually diminishing pressure at the temperature of the body, very little oxygen is given off until the partial pressure of the oxygen is diminished to about 30 mm. Hg (Fig. 474). At this point a large evolution of gas begins, and continues at falling pressure until, at 0 mm. pressure, all the oxyhæmoglobin is dissociated and converted into hæmoglobin. The same observation may be made in the reverse direction. If a solution of reduced hæmoglobin be exposed to gradually increasing pressures of oxygen, it will be found that the greatest absorption takes place between 0 and 30 mm. Hg. After this point, the oxygen is more slowly absorbed up to the point of complete saturation.

Since there is no direct proportion between the partial pressure of the

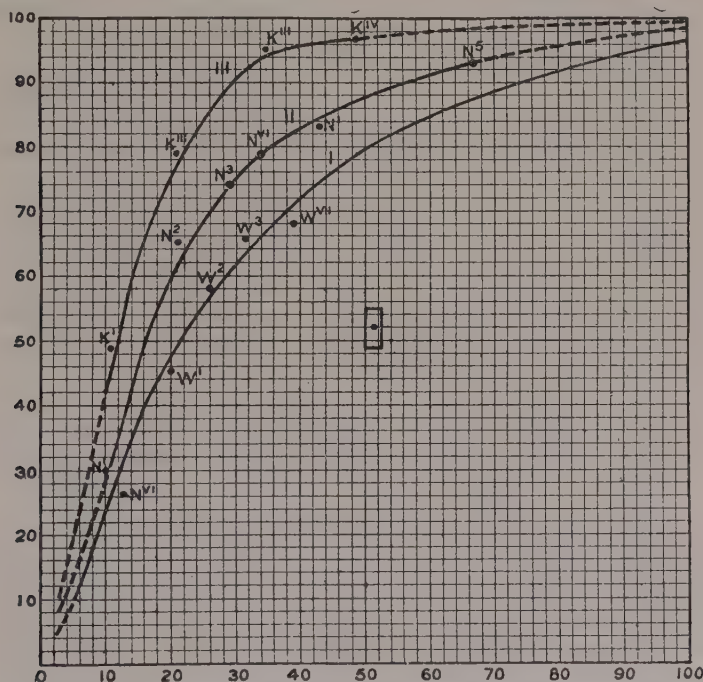


FIG. 474. Dissociation Curves of Oxyhæmoglobin in Various Media.

I, in water; II, in 0.7 per cent. NaCl; III, in 0.9 per cent. KCl.

(BARCROFT.)

oxygen and the amount of it absorbed, it is evident that the oxygen combines with hæmoglobin to form an unstable chemical compound, and that this is not a mere question of solution. This is further proved by the fact that we can displace the oxygen (O_2) from the oxyhæmoglobin by equal volumes of CO or NO.

The relation between the partial pressure of oxygen and the proportion of oxyhæmoglobin formed under varying conditions (percentage saturation), can be investigated in the following way (Barcroft):

A cylindrical glass separating funnel of about 500 c.c. capacity is filled with a gaseous mixture of known composition, containing oxygen. Into it are introduced 2 or 3 c.c. of blood or of hæmoglobin solution. It is then tightly stoppered and immersed in a horizontal position in a water bath at a constant temperature, and slowly revolved. In this way the blood is continually spread in a thin layer over the sides of the vessel. At the end of a quarter to half an hour it will have attained equilibrium with the gaseous mixture. It is then turned into an erect position, so that the fluid can run down into

the neck closed by the stop-cock, whence 1 c.c. may be drawn off for determination of its percentage saturation in a Barcroft apparatus. A sample of the gas is also analysed. The results, plotted as in Figs. 474-476, where abscissæ are pressures of oxygen in mm. Hg, and ordinates are percentage saturations, form what is called the "dissociation curve" of oxyhæmoglobin.

Barcroft has shown that the dissociation curve of oxyhæmoglobin is largely altered by slight variations in the fluid in which the hæmoglobin is dissolved.

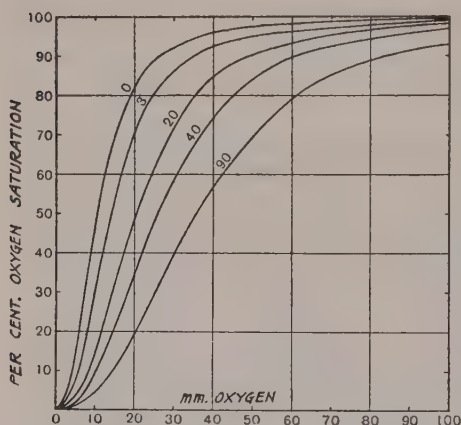


FIG. 475. Oxygen Dissociation Curves of Human Blood, exposed to pressure of 0, 3, 20, 40 and 90 mm. of CO_2 . (BARCROFT.)

The most important of these conditions are (1) the saline content of the fluid, (2) the reaction of the fluid. The influence of dissolved salts on the dissociation curve is shown in Fig. 474.

The differences between the dissociation curves of blood and of oxyhæmoglobin solution, as well as between bloods of different animals, have been shown by Barcroft and Camis to be largely dependent on the saline content of the solution. Thus, human hæmoglobin solution, with a concentration of salts similar to that of dogs' blood, gives the same dissociation curve as normal dogs' blood.

More important is the effect of reaction. In Fig. 475 is represented the influence of varying tensions of carbon dioxide, and in Fig. 476 the effect of slight additions of lactic acid, on the dissociation curve. It will be seen that the more acid the blood, the less firmly is its oxygen held. In other words, carbon dioxide, or other acids, tend to expel oxygen from the blood. It must be remembered that 40 mm. carbon dioxide represents approximately the normal carbon dioxide tension in the blood. At 150 mm. oxygen pressure the blood is practically saturated with oxygen, whatever (within physiological limits) the pressure of the carbon dioxide; but at lower pressures of oxygen, the pressure of carbon dioxide makes a considerable difference to the oxygen saturation. Thus, at an oxygen pressure of 20 mm. Hg the amount of oxyhæmoglobin formed is 70 per cent. when the carbon dioxide pressure is 3 mm., whereas at a pressure of carbon dioxide of 40 mm. the degree of saturation of the hæmoglobin is only 33 per cent. In consequence of this fact, in the tissues where the carbon dioxide tension is high, the

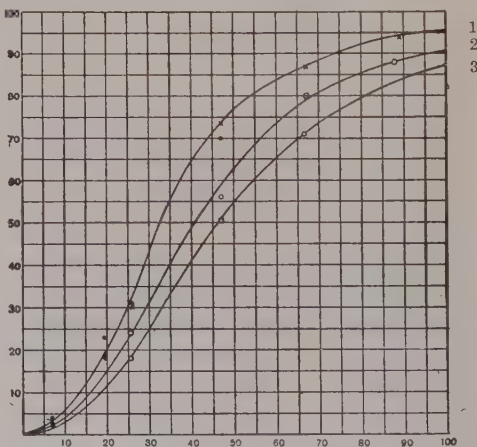


FIG. 476. Dissociation Curves of Sheep's Blood.

1. Normal blood. 2. Blood containing 0.04 per cent. added lactic acid. 3. Blood containing 0.08 per cent. added lactic acid.

oxyhæmoglobin will be dissociated with greater ease, so that oxygen will readily be set free where it is most wanted.

We are now in a position to understand how the oxygen is taken up by the blood, as it circulates round the pulmonary alveoli. Arterial blood, such as that which fills the pulmonary veins and the systemic arteries, is very nearly (*viz.* about 96 per cent.) saturated with oxygen (*i.e.* it contains about 17.8 volumes out of a possible 18.5 volumes per cent.). Venous blood, as passed to the lung, is about 66 per cent. saturated (*i.e.* it contains about 12 volumes of oxygen per cent.) The oxygen pressures are about 100 mm. for arterial blood, and 40 mm. for venous blood, *i.e.* at a tension of 100 mm. the blood is nearly saturated. The tension of oxygen in the alveoli is considerably above this. If we take the oxygen tension in the alveolar air at $\frac{1}{7}$ of an atmosphere, it will still be something over 100 mm. Hence the venous blood brought to the alveoli by the pulmonary artery will, on coming into intimate contact with that atmosphere, take up oxygen from it to saturation, or to a point not far removed from it.

The blood, thus laden with oxygen, is sent from the left side of the heart to all parts of the body. It must be remembered that, neither in the lungs nor in the tissues, does the hæmoglobin come in actual contact with the source of the oxygen, nor with the cells which it is to supply. In both cases, the interchange is effected through the intermediation of the plasma and, in the tissues, of the lymph as well. Since the tissue elements are constantly using up oxygen, they absorb any oxygen that is present in the surrounding lymph. There is, in consequence, a descending scale of oxygen tensions from red blood corpuscle through plasma, vessel wall, lymph and tissue element, and the oxygen is bound to follow this gradient. The cell draws from the lymph, and the lymph from the plasma, so that the oxygen tension in the plasma sinks. This has the same effect as if we put the red corpuscles in a mercurial pump and lowered the pressure of gas. The immediate result is an evolution of oxygen, which is taken up by the plasma, to be in turn passed on to the lymph and the tissue cell.

The rate of passage of oxygen out of the capillaries into the tissue cells must thus be proportional to the difference of tension between the oxygen in the capillaries and that in the cells. If P_b is the oxygen pressure in the capillary blood and P_t that in the tissues, the rate of flow of oxygen from capillaries to tissues must be proportional to $P_b - P_t$. If the blood is to lose oxygen during the whole of this passage through the tissues, we may take for P_b the tension of the oxygen in the venous blood as it leaves the tissues. This is, say, 30 mm. Hg. P_t , the tension of oxygen in the tissues, may be determined in various ways. Verzár's method is based on the following argument. If the oxygen pressure in the tissues is zero, $P_b - P_t$ will equal $30 - 0 = 30$. In this case, any diminution in the tension of the oxygen in the blood will diminish the steepness of fall of pressure between capillaries and tissues, and there would be a corresponding diminution in the consumption of oxygen by the tissues, as determined by a comparison of the oxygen contents in the blood flowing to and away from the tissue respectively. If, however, P_t is positive, *e.g.* 20 mm. Hg, $P_b - P_t$ equals $30 - 20 = 10$. Here a drop in the oxygen tension of the blood might give rise to a corresponding drop in the tension within the tissues: for instance, if the tension in the blood is diminished to 20 mm. Hg, that in the tissues might drop to 10 mm. Hg, and the difference on the two sides of the capillary wall would remain the same, so that the consumption of oxygen by the tissues would be unaltered by changes of the oxygen tension in the blood. Tested by this method Verzár found that the submaxillary gland falls within the

second case, and that its oxygen tension must be but little removed from that of the blood itself. Altering the oxygen tension of the blood, by making an animal breathe a mixture poor in oxygen, does not greatly affect the oxygen consumption in the gland. On the other hand, in resting muscle Verzář found that the oxygen tension is probably zero, so that its consumption could be widely affected by diminishing the oxygen tension in the air supply to the animal.

Krogh has attacked the question in a different manner. In a series of experiments he first determined the rate of diffusion of oxygen through different thicknesses of various tissues (connective tissue, muscle, &c.) under varying pressures. Then, partly on the living muscle, partly on injected specimens, he estimated the relation of the number and size of the capillaries to the intercapillary muscular tissues. He found that extremely small pressure differences were necessary to supply the muscle fibres with oxygen. Some of his results on the guinea-pig are shown in the accompanying Table.

Guinea-pig muscle	c.c. O ₂ per minute per 100 c.c. tissue	Capillaries per mm. ²	Pb — Pt mm. Hg.	Total surface capillary in 1 c.c. muscle	Capacity of capillaries in 100 c.c. muscle
Rest	0.5	31	45	3 cm. ²	0.02 c.c.
	0.5	95	12	8 "	0.06 "
	0.5	270	3	32 "	0.3 "
Massage	0.5	1400	0.04	200 "	2.8 "
Work	5	2500	1.4	390 "	5.5 "
Maximum circula- tion	10	3000	1.2	750 "	15 "

The first thing that strikes us in this Table is the enormous difference between the capillary circulation of resting and that of active muscle. In the resting muscle the majority of the capillaries are empty and collapsed, so that large areas of muscle intervene between the few capillaries in which the circulation of blood is proceeding. Under these conditions, the pressure difference necessary to supply the total oxygen consumed by the muscle. *e.g.* 45 mm. Hg, may fall below the venous oxygen tension, so that in parts of the muscle the oxygen tension may be zero, as maintained by Verzář. After massage, a number of capillaries open, and the number is still further increased by work, so that there may be a hundredfold increase in the number of capillaries in every square millimetre of a cross-section of the muscle. Under these conditions, the passage of oxygen from the capillaries is so facilitated that the oxygen pressure in the muscle tissues becomes practically equal to that of the blood. It would appear that, so far as the supply of oxygen to the muscle is concerned, the increase in the capillary area during muscular exercise is far ahead of the actual needs of the muscle. Krogh suggests that this enormous increase in the number of patent capillaries may be brought about to meet requirements of the muscle other than those for oxygen.

Under normal circumstances the blood never stays in the capillaries long enough to lose the whole of its oxygen. The fraction of the arterial oxygen abstracted, which is called the *coefficient of oxygen utilisation*, varies from tissue to tissue, and from time to time. In states of activity, the venous blood may be more than usually deoxygenated, but generally not more than 0.4 of the arterial oxygen is utilised. If, however, the further supply of oxygen to the blood be prevented, as in asphyxia, the last traces of oxygen may dis-

appear from the blood. The enormous avidity of the tissues for oxygen under these circumstances is shown by the following experiment (Ehrlich). If a saturated solution of methylene blue be injected into the circulation of a living animal, and the animal be killed ten minutes later, it is found, on first opening the body, that most of the organs present their natural colour, although the blood is of a dark blue colour. On exposure to the atmosphere, all the organs acquire a vivid blue colour. This phenomenon is due to an intense reducing activity of the tissues, whereby hydrogen is added to the methylene blue with the production of a colourless reduction product, which on re-exposure to oxygen is reconverted, by loss of hydrogen, into the blue compound. In this reaction the tissue obtains oxygen, for

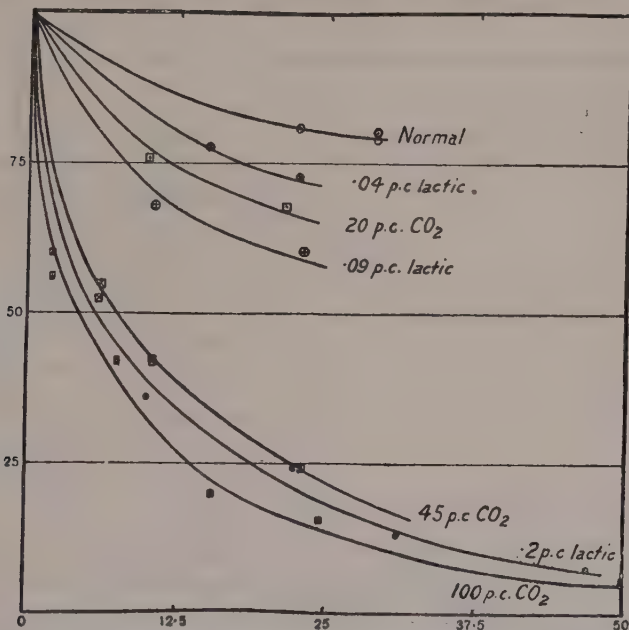


FIG. 477. Curves showing the Rate at which Arterial Blood is Reduced on Bubbling through a Gas free from Oxygen, and the effect on the Rate of the Presence of CO_2 and of Lactic Acid.

Ordinates = percentage saturation of oxyhæmoglobin. Abscissæ = time in minutes. (MATHISON.)

carrying out its oxidative processes, by the decomposition of water, the oxygen from the water being transferred to an oxidisable substance (oxygen acceptor), provided there be present a substance, such as the methylene blue (hydrogen acceptor), which can take up the active hydrogen (*v. p.* 132). If the tissues are able to effect the reduction of a comparatively stable body like methylene blue, it is easy to understand their power of reducing oxyhæmoglobin, which is so unstable that it is decomposed by simple physical means, such as exposure to a vacuum.

As a result of the oxidative changes in the tissues, carbon dioxide is produced, and the tension of this gas in the tissues therefore rises. As Barcroft has pointed out, in cold-blooded animals the dissociation of oxyhæmoglobin with the setting free of oxygen must be largely conditioned by the rise of carbon dioxide tension in the tissues, since at the normal temperature of these animals the evolution of oxygen from hæmoglobin

is extremely slow. The alteration in reaction of the blood, caused by a rise in CO_2 tension or by the presence of small amounts of lactic acid, markedly quickens the rate at which oxyhæmoglobin gives up its oxygen, as is shown in Fig. 477.

THE CARRIAGE OF CARBON DIOXIDE BY THE BLOOD.

Carbon dioxide is soluble in water, and it can easily be calculated that blood at 38°C ., when exposed to a pressure of 40 mm. CO_2 , which is about that of arterial blood, would hold, in a state of physical solution, about 2.7 volumes of CO_2 per 100 c.c. of blood.

It has long been known, however, that blood, as drawn from the body, contains as much as 50 to 60 volumes per cent. of carbon dioxide, held in such a state as to be removable by exposure of the blood in a vacuum, and we have now to inquire why it is that blood is capable of holding amounts

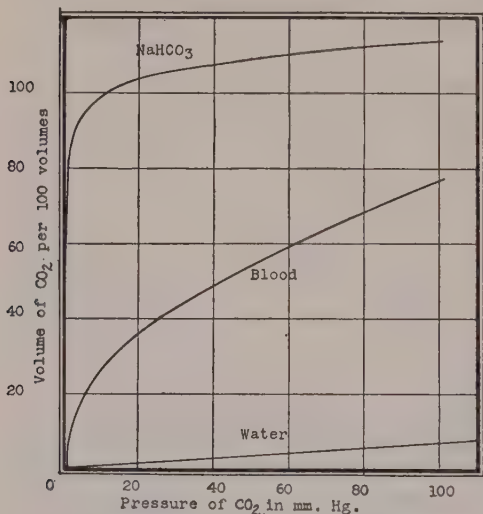


FIG. 478. Comparison between the CO_2 Dissociation Curves of Blood and of Sodium Bicarbonate Solution of a Concentration of 0.0484 N. The amounts of CO_2 held in physical solution in water are also shown (lowest line). (Redrawn from data by PARSONS.)

of carbon dioxide which are so very much greater than can be held in physical solution. A further fact, which has also been long known, is that this carbon dioxide can not only be withdrawn from blood by a vacuum, but can also be expelled from it by the addition of sufficient amounts of strong acids. This suggests at once that the carbon dioxide is held in the blood combined with a base, to form a bicarbonate or carbonate, from which union it is expelled by a more powerful acid, or when the blood is exposed to a vacuum. It should further be noted that, after all possible carbon dioxide has been drawn from blood by exposure to a vacuum, no more can be driven off on addition of a strong acid. One method of expulsion is as good as

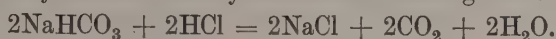
the other, so far as the total yield of CO_2 from whole blood is concerned.

Researches during the past ten years have done much to elucidate the means by which carbon dioxide is carried by the blood, and to show that an interesting chemical mechanism is concerned in it. Perhaps the most valuable information has been obtained by the study of the CO_2 dissociation curves of blood, and of somewhat similar chemical systems. These are made by saturating samples of the fluid with a series of gas mixtures of varying CO_2 pressures, and then determining the volume of CO_2 which can be expelled from the fluid by addition of a strong acid. If we compare the CO_2 dissociation curve of blood with that of a solution of sodium bicarbonate containing the same amount of available base (0.0484 N.), as is shown in Fig. 478, it is evident that there is a very great difference between them. For, whereas all the carbon dioxide is removed from the blood when the pressure of CO_2 is reduced to zero (*i.e.* in a vacuum), it is impossible, by lowering the pressure, to remove from the bicarbonate solution more carbon

dioxide than corresponds to its conversion to carbonate, according to the equation—



i.e. from an aqueous bicarbonate solution only half as much carbon dioxide can be expelled by a vacuum as by addition of a strong acid:—



The carbon dioxide in blood is chiefly bound in the plasma, and is unquestionably present there in the form of an inorganic (chiefly sodium) bicarbonate. This is shown by the fact that the amount of carbon dioxide which can be expelled from the plasma by addition of a strong acid, like sulphuric acid, agrees with the amount of base found by titration with an acid, and further, all this bicarbonate can be removed as such by dialysis. If

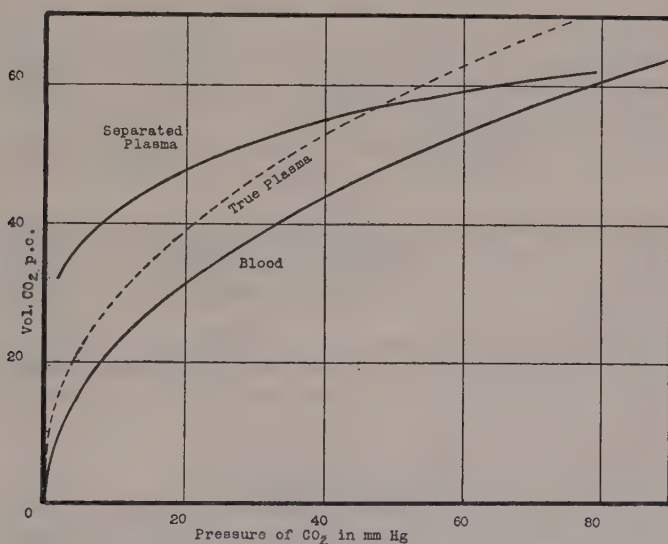


FIG. 479. Comparison between the CO₂ Dissociation Curves of Blood, and of Separated Plasma and true Plasma from the same Blood. (Redrawn from data by JOFFE and POULTON.)

plasma is saturated with carbon dioxide at atmospheric pressure, practically all the available base of the plasma will be present in the form of sodium bicarbonate. The amount of bicarbonate present in the plasma under any circumstances can readily be determined, and is called the "*alkali reserve*."*

If we examine the dissociation curve of blood plasma, we find that separated plasma behaves less like blood than like an aqueous bicarbonate solution. This is confirmed by the well-known fact that, although all the CO₂ can be removed from blood by a vacuum, this cannot be done with blood plasma; after plasma has been thoroughly pumped out *in vacuo*, addition of acid can still set free carbon dioxide from it. It is clear then, that if the carbon dioxide is fixed in the form of bicarbonates in the blood, there must also be in the blood some substance which, while not interfering with the taking up of carbon dioxide by the base when the blood is exposed to

* Strictly speaking, the "*alkali reserve*" is defined as the volume per cent. of CO₂ yielded by the plasma on treatment with acid after the plasma has been previously brought into equilibrium with a gas mixture containing CO₂ at 40 mm. pressure (alveolar air).

increasing pressures of carbon dioxide, will yet act as an acid does, and drive out carbon dioxide, ultimately to completion, as the partial pressure of CO_2 falls.

It is evident that the carrying power of whole blood for carbon dioxide is largely conditioned by *some substance contained in the corpuscles*. It is the corpuscles which *in vacuo* act like the acid, expelling carbon dioxide. This can be proved by the simple experiment of mixing thoroughly well-evacuated plasma with corpuscles, when CO_2 is at once evolved on evacuation.

It is also shown by the comparison of true plasma with separated plasma. The name 'true plasma' is given to plasma drawn direct from the blood, without any change in its gas content. Specimens of true plasma are obtained by centrifuging the blood under a layer of liquid paraffin, to hinder exchange of gases at the surface, and then pipetting off the plasma layer. This represents the plasma which was in a state of equilibrium with the corpuscles of the blood.

Now, if blood be exposed to gas mixtures containing different pressures of carbon dioxide, as in making a CO_2 dissociation curve, it is a simple matter to separate off samples of true plasma corresponding to each pressure of CO_2 , to determine their bicarbonate content, and thus to obtain a curve which may be called the dissociation curve of true plasma. Such a curve represents the carbon dioxide content of plasma which at each point is in equilibrium with the corpuscles.

When this is done, it at once becomes evident that the true plasma behaves in a way entirely different from the separated plasma discussed above. Fig. 479 illustrates this difference.

The true plasma shows a curve which has much the same slope as that for blood, but at a higher level; the plasma of blood, when in equilibrium with its corpuscles, has sometimes a higher percentage bicarbonate content not only than separated plasma, but even than the whole blood. This is because the carbon dioxide-fixing power of corpuscles is less than that of plasma.

The explanation of the way in which the corpuscles confer upon the plasma the power of fixing CO_2 by the formation of bicarbonate is given by experiments by Zuntz and by Hamburger. The latter observer showed that when carbon dioxide is added to blood the following changes occur:—

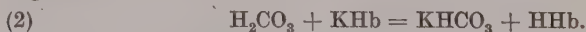
- (1) The bicarbonate content of the plasma is increased.
- (2) The chloride content of the plasma is diminished.
- (3) The chloride content of the corpuscles is increased.

The cations (base) of the plasma and corpuscles are unchanged. Various reactions are concerned in the change, and other subsidiary phenomena occur, but the main changes described above are brought about as follows: Hæmoglobin (especially oxyhæmoglobin) is an acid, and will therefore combine with the base (potassium) of the corpuscles; in presence of a stronger acid, the base will be removed, and the free Hb acid formed. The envelope of the red cells is not permeable to hæmoglobin or to cations, such as K; it is, however, permeable to anions and to carbonic acid, and hence, when blood is treated with carbon dioxide, the following chain of events takes place:—

First, the carbon dioxide passes into solution to form carbonic acid:



and some of this enters the corpuscles. Here it reacts with the potassium salt of hæmoglobin:



We now have the following ions present:

In the plasma, Na^+ and Cl^- .

In the corpuscle K^+ , HCO_3^- , H^+ and Hb^+ ,

but the anions pass through the corpuscular membrane (*v.* membrane equilibria, Chapter VIII.) until an equilibrium is reached, *i.e.* Cl^- enters the corpuscle and HCO_3^- leaves it, and so forms bicarbonate in the plasma.

The Effect of Oxygenation on Carbon Dioxide Carriage. It was found by Christiansen, Douglas and Haldane that reduced blood has a greater carbon dioxide capacity than oxygenated blood (Fig. 480).

In other words, oxygen tends to displace carbon dioxide from the blood,

just as carbon dioxide is known to displace oxygen. They explained this phenomenon on the hypothesis that oxyhæmoglobin is a stronger acid than reduced hæmoglobin, and all subsequent work has confirmed this belief.

The importance of this observation lies in the fact that during its passage along the systemic capillaries not only is carbon dioxide added to the blood, but also oxygen is withdrawn from it, and *vice versa* in passing the lungs.

It is of interest in this connection to attempt to form an opinion of the carbon dioxide absorption curve of blood under the conditions which prevail in the body. Such a curve (for an R.Q. of about 0.8) is shown in Fig. 480, in which portions of the carbon dioxide curves for fully reduced and fully oxidised blood are shown on a large scale. The curve AVB represents the *physiological carbon dioxide absorption or dissociation curve*. At the point A, which may be called the 'arterial point,' since it repre-

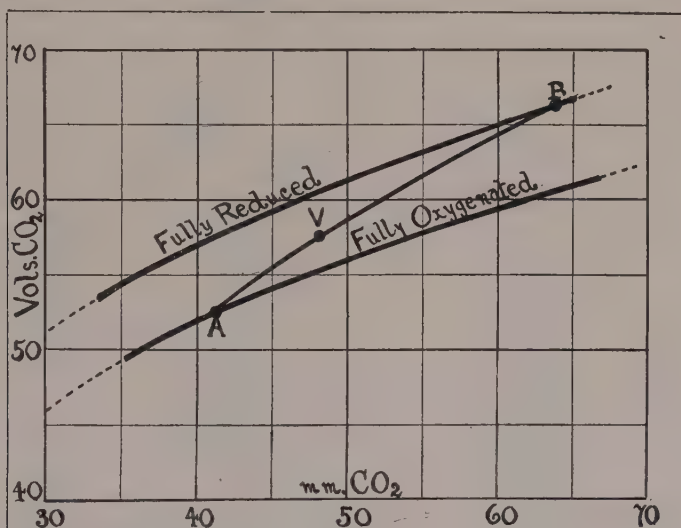


FIG. 480. CO_2 Dissociation Curves of Fully Reduced and Fully Oxygenated Human Blood (only part of the curve is shown). A V B is the physiological curve, along which the CO_2 dissociation operates in the body. (Redrawn from CHRISTIANSEN, DOUGLAS and HALDANE.)

sents the condition in arterial blood, the fully oxygenated blood at 41 mm. CO_2 contains 52.5 volumes CO_2 per cent. The point B represents the condition if the blood were fully reduced; it would then contain at the pressure of CO_2 of 64 mm., not 61 per cent. of CO_2 (as would be the case had there been the same change of CO_2 pressure without loss of oxygen), but 66.5 per cent. Usually the blood does not nearly reach the fully reduced state in passing through the capillaries, but would in most cases stop at a point about in the position indicated by V in the figure. This corresponds to a gain of 5 volumes of CO_2 , and therefore a loss (since the R.Q. is assumed to be 0.8) of about 6.3 c.c. of oxygen. The point V is thus a typical 'venous point.' It will be seen that at least half the increase in CO_2 content of the blood is due to the simultaneous reduction of oxygen content in this instance.

EXCHANGE OF GASES IN THE LUNGS

A fluid gives off gas to, or takes up gas from, any other medium with which it is in contact, according to the relative pressures of the gas. The question arises whether the physical conditions in the lungs are such as to account for the absorption of oxygen by, and the evolution of carbon dioxide

from, the blood in its passage through these organs. In order to answer this question we must know the partial pressures or tensions of oxygen and of carbon dioxide in the alveolar air, in the venous blood coming to the lungs, and in the arterial blood leaving the lungs. In the alveoli, the pressures are given by the analysis of alveolar air. The determination of the gaseous tensions in the blood, however, presents considerable difficulty. It is necessary to bring the blood in contact with a gaseous mixture with which the blood will be in equilibrium. If we know the amount of any gas in this mixture, we know its tension, and therefore the tension of that gas in the liquid.

In all such experiments, the main difficulty is in obtaining a sufficient surface of the blood exposed to the gaseous mixture. The interchange of

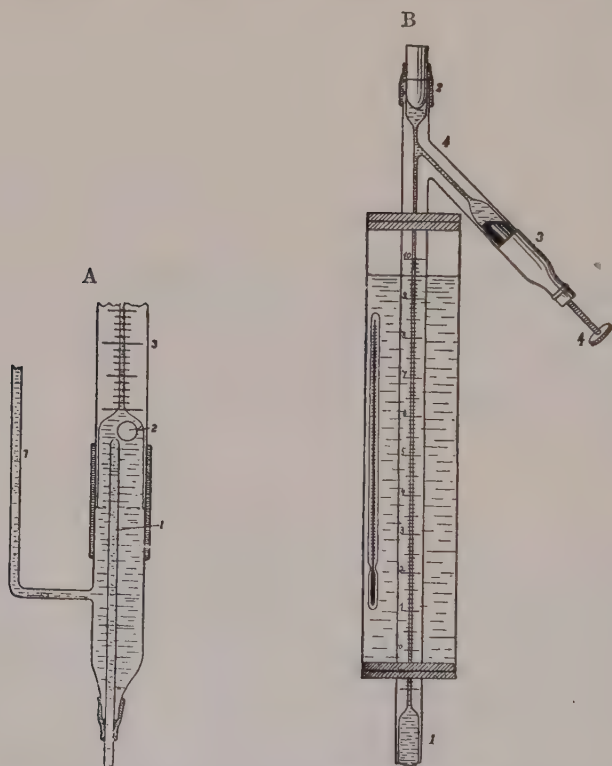


FIG. 481. A. Krogh's Microtonometer. B. Upper part of Microtonometer, showing Capillary Tube into which the Bubble is returned for Measurement and Analysis.

gases is thus very slow, and it is difficult to be certain at any time that the blood and the gas with which it is in contact are really in equilibrium. Krogh therefore adopted the ingenious device of limiting the volume of air to a small bubble, the superficial area of which is large in proportion to its bulk. This bubble, after it has been in a stream of blood for some minutes, is transferred to a special capillary tube, in which its analysis can be carried out.

In such a bubble the equalisation of the tensions takes place with extreme rapidity and only a small quantity of fluid is necessary. The microtonometer consists of the tonometer proper, and the apparatus for the micro-analysis of the gas bubble. In the latter, the measurement of the gas bubble is carried out in a capillary tube, the absorption of carbon dioxide and of oxygen being effected in the usual way with potash and with pyrogallie acid. The tonometer is represented in Fig. 481A. It is kept in a small water-

bath at the temperature of the blood to be examined. The tonometer is filled with saline solution and contains the gas bubble 2, which can be drawn up by means of the screw 4 (Fig. 481B) into the narrow graduated tube 3 (Fig. 481A), where its volume is measured. The blood from the artery or vein, in which we wish to examine the tension of the gases, passes by a cannula through the tube 1, and enters the tonometer as a fine jet. It forces its way up above the gas bubble, which is pressed a little down by the current, and kept oscillating with great rapidity. From the tonometer, the blood flows back through the tube 7 and is collected in a vessel where it can be measured, and afterwards drawn off and reinjected into the animal if necessary. Since the total pressure of the gases in the blood is nearly always lower than atmospheric pressure, it is necessary to keep the pressure in the tonometer also negative.* This is accomplished by means of a mercury valve. During the course of a tonometric experiment, the volume of the gas bubble is measured from time to time, by drawing it up into the graduated tube, and the pressure is regulated until the volume of the bubble remains constant. After five minutes, gaseous equilibrium will have been established between the gas bubble and the surrounding blood, and it is necessary then only to draw it up into the graduated tube and analyse

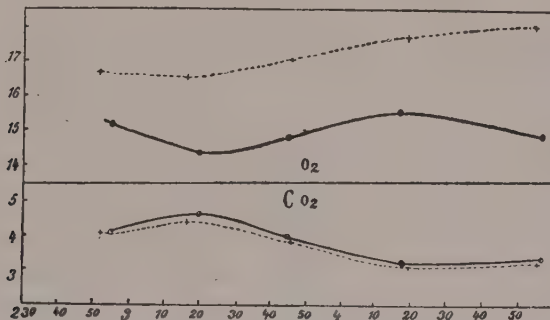


Fig. 482. Tensions of O_2 and CO_2 in Alveoli compared with those in Arterial Blood of Rabbit. (Крогн.)

The dotted lines represent the tensions in the alveolar air, the uninterrupted lines the tensions of the gases in the arterial blood.

it, in order to determine the tension of the gases in the blood. Clotting of the blood is prevented by the injection of hirudin or heparin.

In these experiments, the tension of the air in the alveoli of the animal's lungs, or in the bifurcation of the trachea, was determined by taking samples of the air. The results of the experiments show that the tensions of the gases in arterial blood follow closely the tensions of the corresponding gases in the alveolar air. The tension of carbon dioxide in arterial blood is either identical with, or very slightly above, the tension of the gas in the alveolar air. The oxygen tension of the blood is always lower than the alveolar oxygen tension, and the difference is generally 1 to 2—even 3 to 4—per cent. of an atmosphere. The results of a series of determinations of the tensions of the gases in the blood and alveolar air respectively are given in Figs. 482 and 483. In Fig. 483 A and B (Krogh) the composition of the alveolar air was artificially altered by increasing the percentage of carbon dioxide and of oxygen respectively. It will be seen that in each case there was a corresponding alteration of the tension in the arterial blood, the tension of carbon dioxide being higher and that of oxygen lower, in the blood than in the air, throughout the experiment. We have no direct determinations of the tensions of the gases in the blood of man, though, with the aid of dissociation curves, an

* Otherwise the whole bubble would gradually go into solution and disappear.

approximate valuation of these tensions can be obtained, if we know the degree to which the arterial and venous blood respectively are saturated with oxygen or carbon dioxide. An indirect method is by employing the lung itself as an aerotonometer, since the tensions of alveolar air normally approximate to those of the arterial blood. By a method already described (p. 733) a suitable gas mixture is held for about fifteen seconds in the lungs, and the alveolar air has then the gas tensions of venous blood. By this means the tension of the oxygen in the venous blood was found to be about 40 mm. Hg, and that of the carbon dioxide 6 per cent. = 46 mm. Hg.

The tensions in the alveolar air of man may be taken as follows :

Oxygen	.	.	.	.	.	107 mm. Hg.
Carbon dioxide	.	.	.	.	.	40 „

As the venous blood enters the lungs, there is thus a difference of pressure of about 70 mm. Hg, which will tend to cause a flow of oxygen from

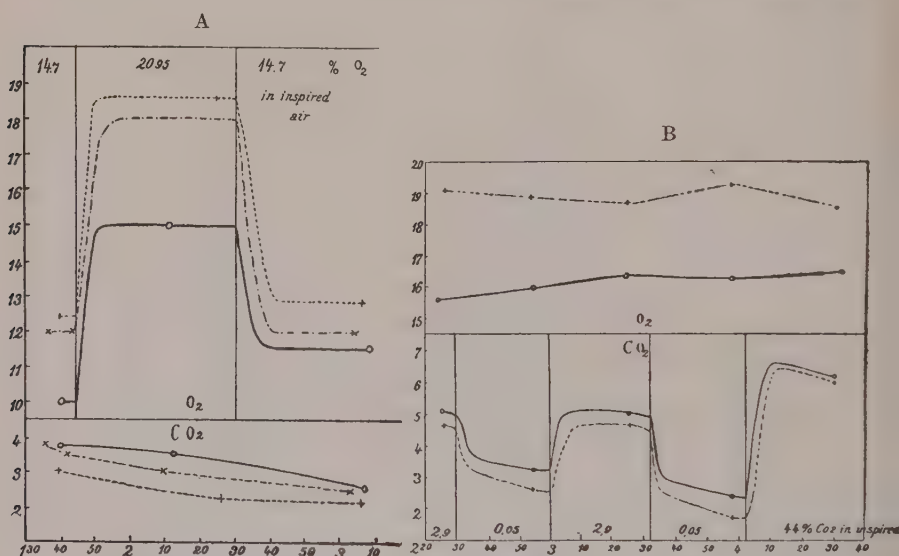


FIG. 483. Tensions of Gases in Alveolar Air and in Arterial Blood.

A. During artificial increase of oxygen tension in alveoli.

B. During artificial increase of CO₂ tension in alveoli.

alveolar air to blood, and a difference of $46 - 40 = 6$ mm. Hg, tending to cause a flow of carbon dioxide from blood to alveolar air. Is this difference sufficient to account for the amounts of gases given off or taken up by the blood in its passage through the lungs? In a state of medium distension, the 3000 c.c. of air contained by the lungs have been estimated to occupy seven hundred million alveoli, each of which has a diameter of 0.2 mm., so that the total surface over which the blood is exposed to the alveolar air amounts to at least 90 square metres (about 1000 square feet). It is important to realise that the blood suddenly spreads out into a layer the thickness of which is not more than that of one blood corpuscle, and is exposed to the air over this huge area, whence it is picked up again and collected into the pulmonary veins. Such a means of facilitating rapid interchange of gases between blood and air we cannot at present imitate artificially. The thickness of the tissue separating this layer of air from the alveolar air is on the average 0.004 mm. Loewy and Zuntz have

calculated the rate at which oxygen would diffuse through a similar layer of tissue, and estimate that, under a constant difference of pressure of 35 mm. Hg, 6.7 c.c. of oxygen would pass in a minute through each square centimetre of the alveolar wall. Through the whole surface of the lung, this would amount to an absorption of 6083 c.c. oxygen. The oxygen actually absorbed by a man at rest amounts to about 300 c.c. per minute, so that the physical conditions allow an ample margin for any increase in the consumption of oxygen; in fact, a difference of pressure of a couple of millimetres would suffice to cause a passage of the 250 c.c. per minute which is required by the resting man. In the same way, it is easy to account for the passage of carbon dioxide in the reverse direction. This gas diffuses through a wet membrane about twenty-five times as rapidly as oxygen, so that a difference of pressure between the blood and the alveolar air amounting to only 0.03 mm. Hg would suffice to cause a passage outwards of the 250 c.c. normally expired per minute.

It is evident that the limitation to the absorption of oxygen is really given by the capacity of the hæmoglobin to combine with it. If we look at the oxygen dissociation curve of blood given on p. 858, we see that the amount of oxygen which can be taken up by blood in the presence of the normal tension of carbon dioxide, *i.e.* 40 mm. Hg, begins to diminish very rapidly when the pressure of the oxygen falls below 50 mm. Hg. Thus, at 40 mm. oxygen pressure, and a carbon dioxide tension of 40 mm., blood is about 75 per cent. saturated, and at 30 mm. it is only 60 per cent. saturated. Under normal circumstances, the blood leaves the lungs about 96 per cent. saturated with oxygen. If the saturation falls to 60 per cent. we should expect to obtain evidence of failure of oxygen supply to the tissues. According to Loewy, the oxygen tension in the alveoli can sink to between 30 and 35 mm. Hg before any signs of oxygen lack make their appearance. These results were obtained by exposing a man, in a state of complete rest, to reduced pressure in an air-chamber. Under these conditions, the slightest muscular exertion would at once tend to cause distress from deficient oxygen supply. The exact percentage of oxygen in the inspired air, which would give an alveolar oxygen tension of 30 to 35 mm., varies with the depth of respiration. Thus, with shallow respiratory movements the pressure may sink to 35 mm. Hg when the inspired air contains as much as 12 per cent. oxygen. If the movements be deeper, the oxygen content of inspired air may be reduced to 9 or 10 per cent. before respiratory distress is observed.

The view that, in the interchange of gases in the lungs, the membrane between the blood and the alveolar air plays simply a passive part is now almost universally accepted. Krogh's experiments show conclusively that the difference between the tensions in the alveoli, and in the blood, respectively, is always such as to allow of the passage by diffusion of oxygen inwards and carbon dioxide outwards from the blood. Moreover, as Krogh points out, the structure of the pulmonary epithelium lends no support to the view that it acts as a secreting membrane. In mammals the cells are of two kinds, *viz.* small granular nucleated cells lying in the interstices of the capillaries, and larger, extremely thin, structureless plates, *without nuclei*, covering the capillaries. In birds, where the gaseous exchange is, of all animals, the most rapid and efficient, the existence of a lung epithelium has never been demonstrated, and the capillaries appear to be almost completely free and to be surrounded with air on both sides.

The view that the pulmonary epithelium actively secretes oxygen was held by Bohr, and it has also been maintained by Haldane that, at all events under circumstances when the oxygen pressure is low in the alveoli, oxygen may be secreted, so as to attain a higher tension in the arterial blood than in the alveolar air. Thus, at high altitudes, Haldane claims that such a secretion can be demonstrated if the subject is given air containing a low percentage of carbon monoxide to breathe. Under these circumstances

the blood is found to contain less CO than when shaken with the same alveolar air (containing CO) *in vitro* ; i.e. the uptake of oxygen had been favoured, and the uptake of CO therefore impeded, in the lungs.

Theoretically, there is no reason to deny the possibility of such powers to the pulmonary epithelium. These data, however, were obtained by a colorimetric method, working with very minute quantities of blood, and have not been generally confirmed. A reinvestigation by Barcroft, of the tensions of oxygen in the blood under such conditions, has failed to lend any confirmation to Haldane's conclusions.

An analogy has been drawn between the processes of gas interchange in the lungs and that in the swim bladder of the fish. Bohr has shown that the gas obtained by puncturing the bladder often contains considerable excess of oxygen. If the bladder be punctured and the fish then left in the water, the gas rapidly reaccumulates, and it is found, on tapping a second time, that the percentage of oxygen is largely increased, and may amount to between 60 and 80 per cent. of the total gases. This reaccumulation of the gases does not take place if both vagi are cut, and is therefore ascribed to a direct secretory activity on the part of the epithelium lining the swim bladder, under the influence of the vagus nerves. However, there is no likeness between the thick typical secreting cells of the swim bladder and the thin structureless plates which separate the capillaries of the lungs from the alveolar air.

EXCHANGE OF GASES IN THE TISSUES

The considerations which determine the exchange of gases between air and blood in the lungs are also operative in determining the gaseous exchanges which take place during the circulation of the blood through the capillaries of the tissues. Blood enters the capillary network as arterial blood, and having, therefore, an oxygen pressure of the order of 100 mm. Hg and a carbon dioxide pressure of the order of 40 mm. Hg. The determination of the pressures of oxygen and carbon dioxide in the tissues is a matter of some difficulty ; we have already seen that the oxygen pressure may vary from one tissue to another, or in the same tissue, from time to time. It is certain, however, that the oxygen pressure in the tissues is always lower than that in the arterial blood and tends to vary inversely as the activity of the tissue.

The carbon dioxide tension of the tissues may be approximately determined by taking the tension of this gas in secretions, such as the urine or bile. It is found to be about 60 mm. Hg, and since in venous blood it is rarely above 50 mm. Hg, there is a gradient of partial pressure of CO₂ from tissues to blood, *viâ* the lymph. The gas therefore passes in that direction by simple diffusion, and the oxygen in like manner passes in the opposite direction, also by diffusion.

THE REGULATION OF THE RESPIRATORY MOVEMENTS

Each movement of inspiration involves the co-ordinated activity of a large number of muscles, and the extent to which they contract will determine the depth of the inspiration. Similarly, if the act of expiration is to take place, they must simultaneously cease to act. The rhythm and extent of the alternate contractions and relaxations of the respiratory muscles are regulated so that the total ventilation of the alveoli shall be sufficient to meet the gaseous exchanges of the body and to keep the composition of the gas in the alveoli at a practically constant level.

The muscles involved in breathing are thrown into activity only by the intermediation of nerves. Each act of inspiration involves a discharge along a number of nerves, *e.g.* the facial to the muscles moving the *alæ nasi*, the vagus to the muscles of the larynx, the branches of the cervical and brachial

nerves to the muscles of the neck, the phrenic nerves to the diaphragm, and the dorsal nerves to the intercostal muscles. The fibres making up these nerves are derived from motor nerve cells, situated at various levels in the medulla and spinal cord. In each act of inspiration or expiration the activities of all these groups of cells must be brought into relation among themselves, as well as with the needs of the organism.

Experiment shows that the co-ordination is effected by the subjection of these motor nuclei to the action of specialised portions of the central nervous system, which act as receiving centres for afferent impressions from the lungs and surface of the body, and which are also endowed with a special sensibility to changes in the composition of the blood circulating through its vessels. These dominant parts are called *respiratory centres*. If the spinal cord be cut across below the seventh cervical nerve roots, the respiratory action of the intercostal and abdominal muscles ceases permanently, although respiration is still continued by the diaphragm and the other muscles supplied by nerves leaving the central nervous system above the point of section. Division of the cord at the first or second cervical nerves abolishes the action of the diaphragm as well, though the movements of the muscles supplied by the facial, vagus, and spinal accessory nerves continue. A section of the brain stem through the mid-brain leaves the respiratory movements unaltered. We must conclude from these experiments that the motor nuclei of the cord are subject to control by impulses originating in the hind brain, and transmitted therefrom down the spinal cord.

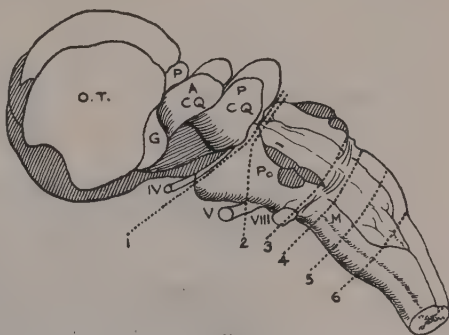


FIG. 484. Diagram of Brain Stem of Cat, showing Levels at which cross section alters the Type of Respiratory Movement. (LUMSDEN.)

Section 1 leaves respiration unaltered.

Section 2, or between 2 and 3, causes development of inspiratory type of respiration.

Section 4 causes gasping respiration.

Section 6 abolishes respiratory movements.

Many experiments have been made with the idea of locating the position of the medullary respiratory centre more accurately. Legallois and Flourens described the respiratory centre as limited to a small area at the level of the apex of the *calamus scriptorius*, which they designated *nœud vital*, on account of the fact that destruction of this area was at once fatal. Later experiments have shown that the centre is not quite so circumscribed. In the first place, it is bilateral, each centre presiding more especially over the muscles of the same side of the body, so that longitudinal section of the middle line does not destroy the respiratory movements. Other observers have located the centre in the situation of the *solitary bundle* ('respiratory bundle of Gierke'), which is made up of the descending branches of the vagus nerve after they have entered the medulla, while, according to Gad, the respiratory centre is diffused over a considerable area of the *formatio reticularis* on either side of the medulla. There is no doubt that this centre is in close connection with the central terminations of the vagus nerves.

According to Lumsden the central respiratory mechanism consists of three parts, viz. :

- (a) A part below the *striæ acusticæ*, which, when working alone, causes gasping respirations.
- (b) A part at the level of the *striæ acusticæ*, which sends out impulses causing a series of prolonged inspirations ('the apneustic centre').
- (c) A part in the upper pons, which inhibits the exaggerated activity of the apneustic centre and so produces normal respiration ('the pneumotaxic centre').

The relative positions of these centres are shown in Fig. 484, and their effects on respiration in Fig. 485.

From the centre on each side, the efferent impulses to the motor nuclei of the respiratory muscles pass down in the deeper portions of the lateral columns of the cord. Hemisection of the cervical cord, *e.g.* on the right side, causes cessation of the contractions of the diaphragm on the same side. There must, however, be commissural fibres joining the motor nuclei on the two sides. If the right phrenic nerve be divided, after hemisection on the left side, the left half of the diaphragm at once commences to contract rhythmically with each respiration (Porter). It is evident that the cessation of respiration after section of the cord is not due to a condition of shock of the lower spinal centres, since it is possible for impulses to pass down the

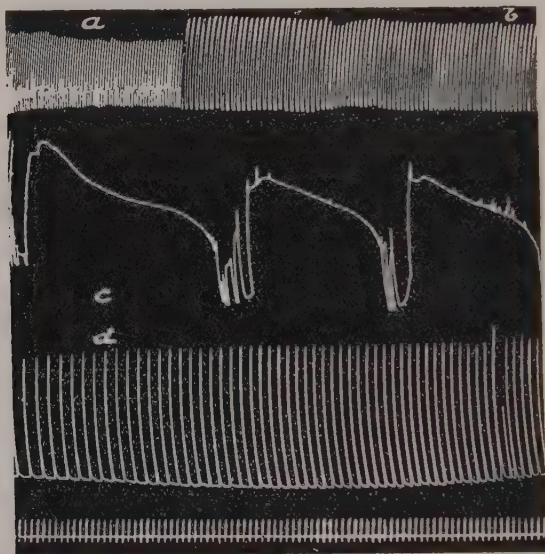


FIG. 485. Tracings of various Types of Respiration in the Cat. (LUMSDEN.)

(a) Normal. (b) After vagotomy. (c) Prolonged inspiratory tonus (*apneusis*) after section 2, Fig. 484. (d) Gasping respiration after section 4. Time tracing = 5 secs. Inspiration upwards.

cord and to cross over to the contra-lateral diaphragm nucleus *immediately* after hemisection of the cord on the side of the nucleus.

Several physiologists, *e.g.* Brown-Séquard, Langendorff, and Wertheimer, have described respiratory centres in the spinal cord. There is no doubt that, if the cord be cut across in the upper cervical region, and artificial respiration maintained for some time, cessation of the respiration may be followed by rhythmic contractions of the respiratory muscles. These are especially marked in young animals, or if the activity of the cord has been heightened by the injection of small doses of strychnine. Careful observation of the movements shows, however, that they cannot be spoken of as *respiratory*, since, although rhythmic, they are not co-ordinated. These experiments show merely that the motor centres of the cord can enter into rhythmic activity under the influence of asphyxial conditions.

THE AUTOMATICITY OF THE RESPIRATORY CENTRE

We have now to inquire whether the activity of the centre is reflex or automatic. It was found by Rosenthal that rhythmic respiratory move-

ments are maintained, even after complete section of the brain stem at the level of the superior corpora quadrigemina, section of the cord at the level of the seventh cervical nerve, and division of both vagi and of the posterior roots of all the cervical spinal nerves. It is true that if the sections of the brain stem be placed as low as the *striae acusticae*, the respiratory movements are profoundly modified and give place to a series of inspiratory spasms, but this is to be explained as due to the removal of an important superior centre.

The respiratory centre tends to respond to all stimuli, continuous or rhythmic, by means of rhythmic discharges, and there can be no doubt that, if we consider the medulla together with the rest of the hind brain, we are justified in regarding its activity as automatic, *i.e.* as not fundamentally reflex.

When we speak of the automatic activity of the respiratory centre, we imply that, in the same way as the heart, its activity is dependent on the normal composition of the blood circulating through its vessels. In this case, however, it is the gaseous contents of the blood which are of supreme importance.

THE CHEMICAL REGULATION OF THE RESPIRATORY MOVEMENTS

If, the nervous centres being intact, the proper aeration of the respiratory centre be interfered with in any way, the respiratory movements increase in strength and frequency, and if the disturbing factor be not removed, the animal dies, presenting a train of phenomena which are classified together under the term 'asphyxia.'

The phenomena of asphyxia may be divided into three stages :

(1) In the first stage, that of *hyperpnœa*, the respiratory movements are increased in amplitude and in rhythm. This increase at first affects both inspiratory and expiratory muscles. Gradually, the force of the expiratory movements becomes increased out of all proportion to the inspiratory, and the first stage merges into :

(2) the second, which consists of *expiratory convulsions*, in which almost every muscle of the body may be involved. Just at the end of the first stage consciousness is lost, and almost immediately after the loss of consciousness, we may observe a number of phenomena extending to almost all the functions of the body, some of which have already been studied. Thus the vasomotor centre is excited, causing universal vascular constriction. There is often also secretion of saliva, inhibition or increase of intestinal movements, constriction of the pupil, and so on.

(3) At the end of the second minute after the stoppage of the aeration of the blood, the expiratory convulsions cease almost suddenly, and give way to *slow deep inspirations*. With each inspiratory spasm, the animal stretches itself out and opens its mouth widely, as if gasping for breath. The whole stage is one of exhaustion : the pupils dilate widely, and all reflexes are abolished. The pauses between the inspirations become longer and longer, until, at the end of four or five minutes, the animal takes its last breath.

If we increase the activity of the centre, and therefore its gaseous interchanges, by warming the blood in the carotid arteries, there may be a considerable quickening of respiration unaccompanied by any deepening, a condition which is spoken of as *tachypnœa*. On the other hand, we may slow the respiratory movements by placing a small piece of ice on the floor of the fourth ventricle.

In the production of the phenomena of asphyxia, two factors must be at work. In the first place, there is an accumulation of carbon dioxide in the blood bathing the centre, or an increased tension of this gas in the centres themselves, as a result of either deficient excretion or increased production. On the other hand, the centre is deprived of oxygen, either by failure of renewal of the oxygen supply or by increased using up of this gas in the metabolism of the centre. The question arises, which of these two changes is responsible for the different physiological events which characterise asphyxia? At various times the stimulus for the respiratory centre has been ascribed, either to the increased tension of carbon dioxide, or to the diminished tension of oxygen in the centre. Increase of this stimulus augmented the activity of the centre and caused hyperpnœa, reduction lowered its activity, so that breathing was suspended—a condition called *apnœa*. Recent work, especially by Haldane and his pupils, has shown that there is an element of truth in both views—that indeed the respiratory centre can be excited either by excess of carbon dioxide or by lack of oxygen, but that its sensitivity to

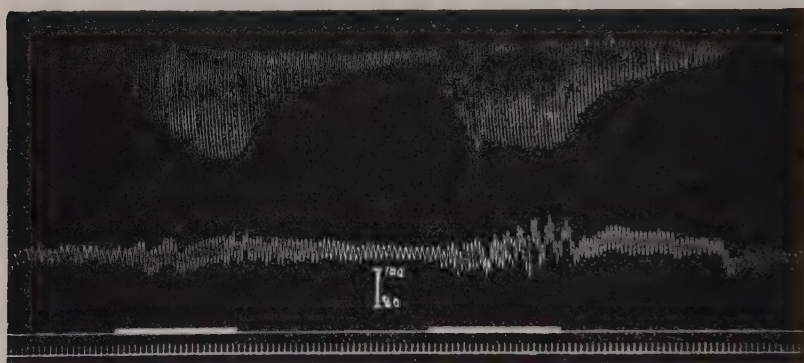


FIG. 486. Effect of CO_2 on Respiratory Movements of Rabbit. (Scott.) Upper line, tracing of diaphragm slip (Head's method). Lower tracing, carotid pressure. During the first period indicated on the signal line the animal breathed 9.6 per cent. CO_2 in air, and during the second period 10 per cent. CO_2 with 33 per cent. oxygen. Time tracing = 2 secs. Scale = mm. Hg blood pressure.

carbon dioxide is by far the more important factor in the determination of the increased respiratory movements in asphyxia, and is the only chemical variable in the blood which can be regarded as playing a large part in the regulation of the respiratory movements under normal conditions. This factor is well brought out if we investigate the effect on the respiratory movements of altering the tensions of the two gases in the air breathed. If, by this means, we alter the tension of the two gases in the alveolar air, we may assume that the tensions of the gases in the arterial blood leaving the lungs are similarly changed. The results of such experiments are very striking. Even a slight increase in the percentage of carbon dioxide in the air causes an increase, first in the depth and later on in the rhythm, of respiration (Fig. 486). This is shown in the following Table (Haldane), which represents the average depth and frequency of the respirations when the subject was breathing normal air and air charged with varying percentages of carbon dioxide. For instance, a rise of carbon dioxide in the atmosphere to 2 per cent. increases the depth of respirations by 30 per cent., and the total alveolar ventilation by 50 per cent.

If we examine the last column of figures in this Table, representing the percentage of CO_2 in the alveolar air, it will be seen that, in spite of

the very large variations in the air breathed, the alveolar content of CO_2 remained practically constant until the CO_2 in the atmosphere was increased

Percentage CO_2 in inspired air	Average depth of respirations	Average frequency of respirations per minute	Ventilation of alveoli with inspired air (normal = 100)	CO_2 percentage in alveolar air
0.04	673	14	100	5.6
0.79	739	14	(6.60 litres per min.) 116	5.5
2.02	864	15	153	5.6
3.07	1216	15	226	5.5
5.14	1771	19	498	6.2
6.02	2104	27	857	6.6

to such an extent that the processes of compensation were no longer efficient. We must conclude, therefore, that the respiratory centre is so arranged as to react to the slightest increase of CO_2 tension in the blood, any increase in this gas giving at once a compensatory increase in depth and frequency of respiration, so that the alveolar CO_2 pressure may be maintained almost constant.

That it is the partial pressure of CO_2 in the alveolar air and therefore in the blood bathing the centres, and not the percentage amount of this gas in the air, which is really the determining factor, is shown by a comparison of the composition of the alveolar airs of subjects under different atmospheric pressures.

In calculating the partial pressure from the percentage composition and barometric pressure, deduction of 50 mm. is made from the latter to allow for the tension of aqueous vapour at body temperature. Thus at sea level (barometer = 755 mm.), the alveolar CO_2 pressure of the subject from which the above table was derived was

$$\frac{5.6}{100} \times 705 = 39.5 \text{ mm.}$$

Hg. When the subject was placed in an air-chamber compressed to a pressure of 1261 mm., the mean percentage of CO_2 in the alveolar air was 3.42, corresponding, however, to a tension of

$$\frac{3.42}{100} \times 1211 = 41.4 \text{ mm.}$$

Hg. At the top of Ben

Nevis, where the barometric pressure was 646 mm., the percentage of CO_2 in the alveolar air rose to 6.6, corresponding to a tension of $\frac{6.6}{100} \times 596 = 39.3$

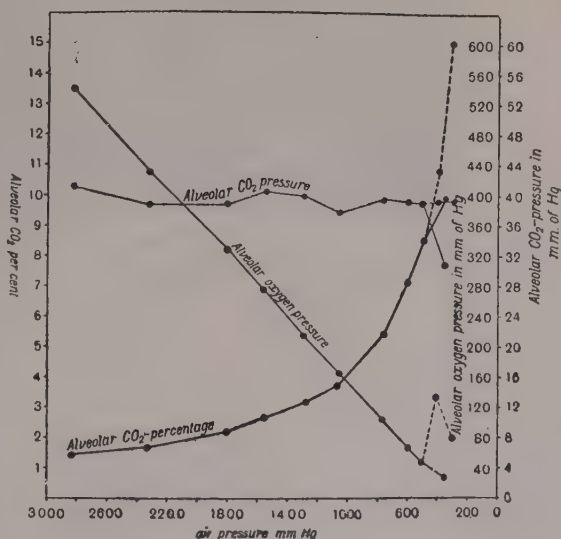


FIG. 487. Effects of Alterations in the Barometric Pressure on the Alveolar CO_2 Tension, the Alveolar CO_2 Percentage and on the Alveolar O_2 Tension. Note that the excitant effects of O_2 lack are not seen until the atmospheric pressure falls below 500 mm. Hg. (BOYCOTT and HALDANE.)

mm. Hg. Thus, the pressure of CO_2 in alveolar air remains practically constant with widely varying limits of atmospheric pressure as well as with very different percentages of CO_2 in the inspired air, showing that the reactions of the organism are directed so as to maintain, by alterations in the respiratory depth and rhythm, a constant *tension* of this gas in the alveoli, and therefore in the arterial blood.

Very different are the phenomena observed on alteration of the partial pressure of oxygen (Fig. 487). Here, within wide limits, the partial pressure of oxygen in the alveolar air is determined by its pressure in the inspired air. Thus, if we take the same series of observations, with a pressure of 646 mm..

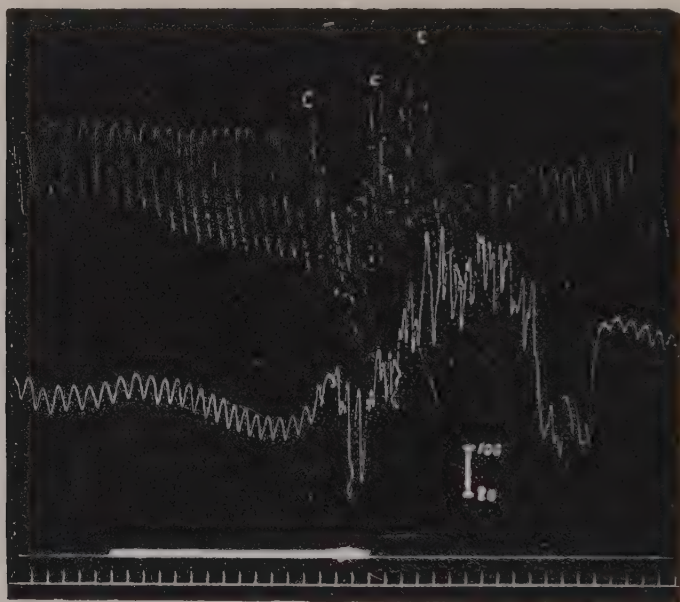


FIG. 488. Effects of Oxygen Lack. (SCOTT.)

Upper tracing, diaphragm slip; lower tracing, carotid blood pressure. During time indicated by signal, 5 per cent. oxygen in nitrogen was inhaled. c = convulsion.

the *percentage* of oxygen in the alveolar air was 13.19, corresponding to a *tension* of $\frac{13.19}{100} \times 596 = 78.6$ mm. Hg. At an atmospheric pressure of 755 mm. the percentage of oxygen in the alveolar air was 13.97, corresponding to a tension of 98.5 mm., which we may take as the normal figure at the sea-level. In air compressed to a pressure of 1261 mm. the percentage of oxygen was 16.79, corresponding to a tension of 203 mm. of oxygen.

Similar results are obtained by altering the percentage of oxygen in the air breathed. The oxygen tension or percentage in the inspired air can be lowered from its normal of 20.93 to 13 per cent., at which the alveolar oxygen is about 8 per cent. (= 57 mm. Hg), without altering in any way the depth or rhythm of respiration, and, in fact, without any change being noticed by the individual who is the subject of the experiment. With a further reduction of the oxygen content, however, there is increased pulmonary ventilation (Fig. 488), but the diminution in oxygen may be pushed to such an extent that the patient becomes blue from the deficient oxygenation of his hæmoglobin, without any considerable distress being caused. In fact, in many cases, the

subject of such an experiment may lose consciousness suddenly, before he has felt serious discomfort.

The difference in the sensitiveness of the centre to increase of carbon dioxide and lack of oxygen respectively, is well shown by an experiment of Haldane's, in which the same person breathed in and out of a bag, in the first place allowing the carbon dioxide produced in respiration to accumulate, and in the second, removing the carbon dioxide by means of soda lime, so that the sole effect of respiration was to produce a continual diminution in the percentage of oxygen. In the first case, when the carbon dioxide was allowed to accumulate, it was found that intolerable hyperpnœa was produced when the content of the bag had reached 5.6 per cent. carbon dioxide with 14.8 per cent. oxygen. When the carbon dioxide was absorbed, it was possible to breathe in and out of the bag for a much longer period. No hyperpnœa was produced, and the experiment was stopped as soon as the subject was becoming blue in the face and experienced slight throbbing in the head. The pulse frequency had gone up from 80 to 108. The bag was found to contain no carbonic acid and only 8.7 per cent. oxygen. In another similar experiment the oxygen had been reduced to 6.7 per cent. before it was necessary to stop the experiment.

We must conclude that the respiratory centre is peculiarly sensitive to variations in the pressure of carbon dioxide, and that these variations are the chief ones which determine the normal depth and rhythm of the respiratory movements. Although the respiratory centre, in common with the rest of the central nervous system, is sensitive to, and can be excited by, lack of oxygen, this quality is rarely brought into play. Under all ordinary circumstances, an increased need for oxygen is associated with an increased production of carbon dioxide in the body, and the augmentation of respiration, produced by the excitatory effect of a small excess of carbon dioxide tension in the blood, suffices also to provide fully for the increased needs for oxygen.

As an example of a normal adaptation, we may take the changes in respiration which occur in an animal as the result of muscular exercise. During activity, the blood, in passing through the lungs, will not be able entirely to get rid of the excess of the carbon dioxide, and will reach the respiratory centre with a slightly increased CO_2 tension. The respiratory centre is thus stimulated, and the increased pulmonary ventilation thereby produced lowers the alveolar carbon dioxide pressure, until a point is reached at which an equilibrium is maintained between the effect of the increased production of carbon dioxide in raising the arterial carbon dioxide tension and that of the increased respiratory activity in lowering it. Under these circumstances it is found that the increased consumption of oxygen in the contracting muscles is more than compensated.

When the exercise is violent, so that the animal or man runs into 'oxygen debt,' or when the individual breathes air of low oxygen pressure, the respiratory movements may even be increased to such an extent that the tension of carbon dioxide in the blood falls below normal. Under these circumstances, some other mechanism must be invoked to explain the increased breathing. An important factor, no doubt, is the hydrogen-ion concentration of the arterial blood. Usually an increase in the hydrogen-ion concentration of the blood causes a corresponding augmentation of the respiratory ventilation. During rest or moderate exercise, the reaction of the blood is a function of its CO_2 tension. With violent exercise, two acids, namely carbonic and lactic acids, contribute to the change in hydrogen-ion concentration. If enough lactic acid is produced, the respiratory movements may be augmented to such an extent that the CO_2 tension in the blood falls below normal and yet the hydrogen-ion concentration may be raised, because so much bicarbonate has been neutralised by the lactic acid.

The first phase in the phenomena of asphyxia is conditioned simply by the changes in the carbon dioxide tension. A little later, the gradual exhaustion of oxygen in the blood supplied to the centre begins to make itself felt. The respiratory centre shares with the rest of the central nervous system a sensitiveness to the absence of oxygen, deprivation of oxygen having first an excitatory, and later a paralytic, effect. In asphyxia, the first centres to feel this effect are those of the cortex, and during the first stage there is mental excitation, terminating rapidly in abolition of consciousness. During the second stage there is a discharge of energy, which spreads throughout the whole nervous system, beginning in the bulbar centres and causing a great rise of blood pressure, with slowing of the heart, and extending thence to all the spinal centres with the production of muscular spasms. At this stage too, there is a discharge of impulses causing contraction of the pupil, and a discharge along the whole sympathetic system, producing the various phenomena of vaso-constriction, erection of hairs, sweating, salivation, which are generally brought about by stimulation of different parts of this system. The phenomena of the third stage are due to exhaustion of the nerve centres, accompanied or preceded by exhaustion and dilatation of the heart, the circulation failing before the excitation of the lower centres has entirely

come to an end. In this third stage, it is impossible, even by the strongest stimuli, to evoke any reflex.

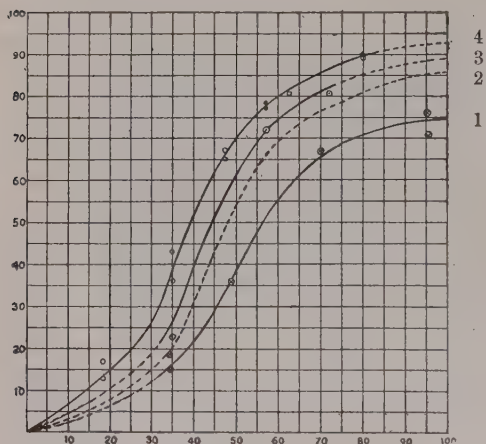


FIG. 489. Oxygen Dissociation Curve of Defibrinated Cats' Blood.

1. Cat I, after partial occlusion of trachea and fifteen minutes' breathing of gas of increasing poverty in oxygen.
4. Cat II, at beginning of experiment.
3. Cat II, after fifteen minutes' gas respiration.
2. After twenty-one minutes' ditto.

at first become more alkaline, and yet the centre is excited to an abnormal degree. Nor can we ascribe the stimulation in oxygen lack to the presence of lactic acid in the blood, though this undoubtedly occurs, even to such an extent as greatly to modify the oxygen dissociation curve of the blood (Fig. 489). Yet when the exposure to low oxygen tensions is of short duration, no large amount of lactic acid is produced in the blood.

It is more satisfactory to regard the excitation of the cells of the respiratory centre as dependent upon a complex heterogeneous equilibrium between these cells and the blood, as is done by Gesell. According to this view, the cells of the respiratory centre are excited when their protoplasm becomes more acid. Like muscle and other cells, these cells are believed to be continually producing lactic acid, which is normally being removed, chiefly by oxidative processes, but partly by passing out into the blood. There will thus be a state of balance between the rate of production and the rate of removal of the acids (lactic and CO_2) in the nerve cells, and on this balance will

Considerable discussion has taken place as to the exact nature of the stimulus to the respiratory centre, especially that brought about by want of oxygen. The centre is particularly sensitive to variations in the CO_2 pressure of the blood. For instance, when the CO_2 pressure of the alveolar air is raised by only 1.5 mm., the breathing is doubled. This would cause an increase of pH of the blood of only 0.012. Can we, then, regard the cells of the respiratory centre as exquisitely sensitive to the H-ion concentration of the blood, and consider this as the real stimulus? The answer is that we cannot, because, under some conditions, the centre behaves as though it were indifferent to the blood reaction. For instance, in acute oxygen lack, the blood may

depend the reaction, and through that, the excitability, of the respiratory centre cells. A lowered oxygen tension in the cells of the centre will lead to a diminished rate of oxidative removal of lactic acid (as with any other cells), and consequently to its accumulation in the cells, which will cause their H-ion concentration to rise. If the oxygen utilisation of the nerve cells is abruptly checked, as by the injection of a trace of cyanide into the blood, the same thing happens at once, and there is an instant and great hyperpnoea, though it may take a minute or two before there is a pronounced increase of the lactic acid content of the blood. Addition of lactic acid or carbon dioxide to the blood, with increase of its hydrogen ion concentration, will also indirectly affect the reaction of the cells of the centre. In the long run the addition of any strong acid to the blood is equivalent to addition of carbon dioxide, since it displaces that gas from the bicarbonate of the plasma; carbon dioxide diffuses so readily through the walls of all animal cells that it very speedily affects the hydrogen-ion concentration of the cell interior, and it is probably this penetrating power which explains the dominant rôle played by carbon dioxide in regulating the respiration.

This view, therefore, brings under one head all the several factors which we know to act upon the respiratory centre, namely, tension of carbon dioxide, presence of acids in the blood and considerable diminution of oxygen supply to the cells, and we see that it is not correct to regard any one of these as the sole operative factor.

Since the animal has developed a mechanism by which the reaction of the blood can be rapidly adjusted by varying the excretion of carbon dioxide, whilst the excretion of other acids is relatively slow, carbon dioxide may be regarded, as in effect, the normal respiratory stimulant; and so far we may agree with Henderson in regarding carbon dioxide as maintaining the activities of the various nerve centres at their normal level. But it is the hydron concentration of these cells which appears to be the essential factor, and the acid substances which accumulate in them during oxygen lack are equally efficacious, but not so convenient. Thus their accumulation is not a steady process like that of carbon dioxide, but, as Mathison pointed out, commences suddenly at a time when the executive side of the nerve cell is feeling the effect of oxygen starvation, so that the cell may be too much disorganised to respond to stimulation. "The broad margin of safety protecting the organism against paralysis of its cells by oxygen starvation is assured by the sensitiveness of the medullary centres to hydrogen ion concentration and therefore to carbon dioxide in common with other acids."

On the other hand, it must be remembered that excessive production of hydrogen ions may finally result in a condition of paralysis, which, in the nervous centres, is expressed by narcosis. This is probably one reason for the paralysis of respiration caused when the oxygen pressure falls below a certain limit. These effects can be removed only by a free supply of oxygen.

THE REFLEX NERVOUS REGULATION OF RESPIRATION

Although the sensibility of the respiratory centre to CO_2 is the most important factor in determining the depth and rhythm of the respiratory movements, the condition of the respiratory centre itself is modified in a large degree by impulses arriving at the centre along both vagi. Through other sensory nerves of the body the respiratory movements can be altered reflexly, but under normal circumstances it is only through the vagi that a continuous stream of impulses passes to the centre, so that every respiratory movement is modified by these impulses.

The respiratory movements may be registered by means of a tambour applied to the chest, communicating with another tambour provided with a lever, which is arranged

to write on a blackened surface; or a side tube to a cannula in the trachea may be connected with the registering tambour. In the first case, movements of the thorax are registered; in the second, changes of intra-pulmonary pressure.

When it is wished to study the effects of artificial distension or collapse of the lungs we may use the method described by Head. In the rabbit, a slip of the diaphragm on either side of the ensiform cartilage is so disposed that the end of it may be freed, without injury to its blood- or nerve-supply, and attached by a thread to a lever. This slip contracts synchronously with the rest of the diaphragm, so that it serves as a sample of the diaphragm, the contractions of which may be recorded, uninfluenced by passive movements of the chest wall, or by artificial changes of intra-pulmonary pressure.

If, while the respiratory movements are being recorded, both vagi be divided,* a marked change in the respiratory rhythm is at once seen. The first effect is an increased inspiratory tonus, but this rapidly disappears, and the respiratory movements become less frequent, but are increased in amplitude. If, now, the central end of one of the vagi be stimulated with an interrupted current, the respiration may be quickened or, as is more commonly the case, the inspiratory movements may be increased at the expense of the expiratory, so that finally a condition of inspiratory standstill is produced, and the slip of the diaphragm enters into prolonged contraction.

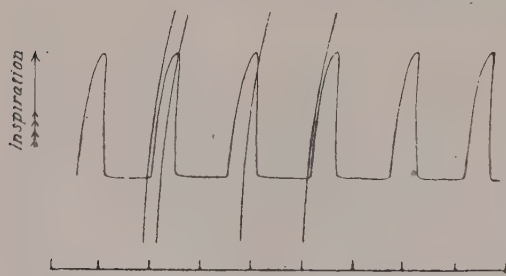


FIG. 490. Normal Tracing of Diaphragm Slip.
(Head's Method.)

With a very weak stimulus, it is sometimes possible to produce inhibition of the inspiratory movements, and this is the invariable result of passage of a *constant* current through the vagus, in an ascending direction. This effect may be more strikingly brought about by

stimulation of the central end of the superior laryngeal nerve, which produces first an inhibition of inspiration, so that the respiratory muscles come to a standstill in the position of expiration, and then a forcible contraction of the expiratory muscles. This illustration of the presence of afferent expiratory fibres in the superior laryngeal nerve is not confined to laboratory experience, but is constantly occurring in everyday life. The superior laryngeal nerve supplies sensory fibres to the mucous membrane of the glottis, and we know that the slightest irritation of these fibres—the presence of a crumb or a particle of mucus—causes forcible expiratory spasms, with spasmodic closure, of the glottis, which we term a cough.†

So we see that the vagus nerve contains afferent fibres with two distinct functions. Stimulation of the one kind stops inspiration and produces expiration; stimulation of the other stops expiration and produces inspiration. Since section of both vagi causes slowing of respiration, impulses which exert some influence on the respiratory centre and quicken respiration,

* The 'division' of the vagi is best effected by putting them on a hooked copper wire, the upper end of which is inserted in a freezing-mixture. In this way, complete functional division of the nerves is obtained, without any excitation. If the nerves be cut, a certain amount of stimulation takes place, in consequence of the closure of the demarcation current produced by the cross section.

† It must not be imagined that the fibres of the superior laryngeal nerves are concerned in the reflex maintenance of the normal respiratory rhythm. They are cited here merely because the result of their stimulation resembles that which would be caused by stimulation of the analogous expiratory fibres which run in the trunk of the vagus from the *lungs* to the respiratory centre.

must travel up the vagi from the lungs. The respiratory movements cause an alternate distension and contraction of the lungs, and it appears that it is these changes in the volume of the lungs which start the accelerating impulses that travel up the vagus nerves. To test the truth of this hypothesis, it is necessary to study the two phases of respiration separately; that is, to see the result, on the respiratory movements, first of distension, and secondly of collapse, of the lungs. These may be shown by simply closing the trachea at the end of inspiration or of expiration. The results of such an experiment are shown in Fig. 491.

A still more marked effect is produced if the lungs, by means of a tube in the trachea, be artificially inflated or if air be sucked out of them. The inflation produces an instantaneous and complete relaxation of the diaphragm (Fig. 492) which by clamping the tracheal tube may be prolonged for several seconds, while sucking air out of the lungs causes a tonic contraction of the diaphragm (Fig. 493). Somewhat similar results may be obtained by repeatedly inflating or deflating the lungs (positive and negative ventilation). The effects here are complicated by the fact that one is dealing in both cases with alternating movements of the lungs—viz.:—expansion and contraction, both of which will have an influence on the respiratory centre. Moreover, repeated forcible inflation of the lungs lowers the carbon dioxide tension of the alveolar air. As a result of repeated

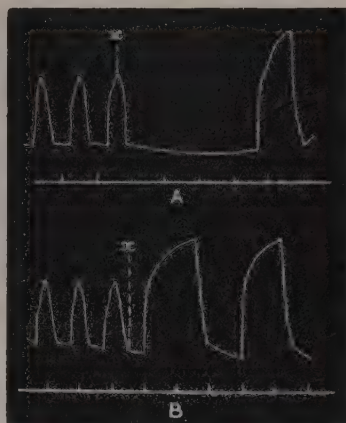


FIG. 491. Effects of Distension and Collapse of Lung. Contraction of diaphragm slip of rabbit. Upward movement = inspiration (contraction). (FOSTER).

In A, the trachea is closed at *x*, the height of inspiration; a long pause follows, and finally an inspiration (a very powerful one) sets in.

In B, the trachea is closed at the end of expiration, *x*; powerful inspirations follow at once.

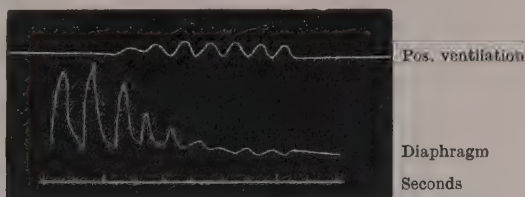


FIG. 492. Positive Ventilation. (HEAD.)

Under the influence of positive ventilation, the inspiratory contractions of the diaphragm become less and less till they disappear completely.

ventilation we may obtain a condition of respiratory standstill. In this condition, however, as we shall see later, the determining factor is chemical rather than mechanical.

These inhibitory and augmentor effects of changes in the volume of the lung must also result from the normal movements of these organs in respiration. Let us consider, for instance, what will happen if the influence of the two vagi could be suddenly thrown in after these nerves have been divided. (This experiment can in fact be realised more or less completely if the functional division of the vagi be effected by cooling or by ether narcosis.) The animal would be breathing slowly and deeply. If, at the beginning of an inspiration, the vagi became functional, the expansion of the

lungs caused by the inspiratory movement would send inhibitory impulses up to the vagus centre, which would stop the movement of inspiration.

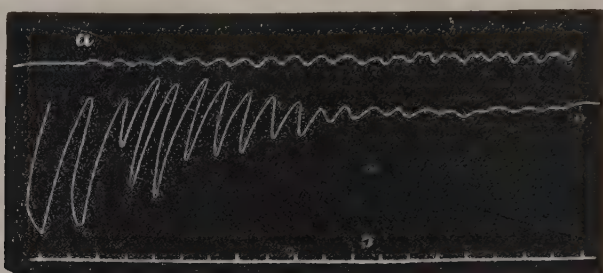


FIG. 493. Negative Ventilation. (HEAD.)

At a negative ventilation was commenced. The expiratory relaxation of the diaphragm is seen to become more and more incomplete, until it finally enters into continued contraction.

The movement of expiration would then begin, but the collapse of the lungs thereby produced would itself send impulses up the vagi, which would tend to excite an inspiratory movement. Both inspiration and expiration would therefore be shortened, and the successive movements would follow one another at a shorter interval than if the vagi were not functional. In this way, under normal circumstances, the *rhythm* of the respiratory centre must be determined reflexly through the agency of the vagi, while the chief factor in determining the total pulmonary *ventilation* is, as we have seen, the carbon dioxide tension of the blood.

In the foregoing account we have spoken of the expiratory and inspiratory effects of the vagus as if they were of equal importance. It seems probable, however, that the expiratory impulses, started by the inspiratory movement, plays a more prominent

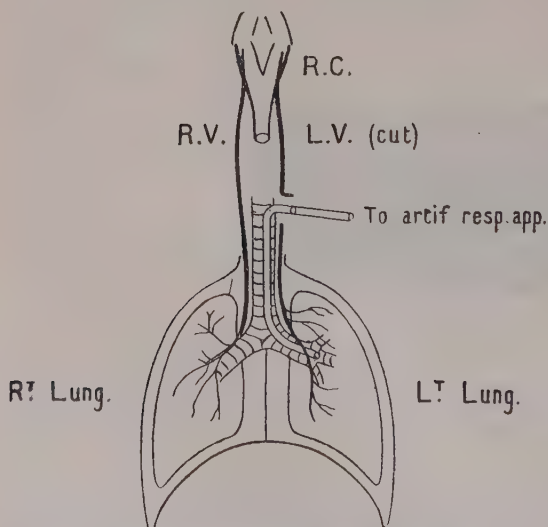


FIG. 494. Diagram to illustrate Head's Experiment on the Effect of Collapse of the Lung.

R.C. Respiratory centre. R.V., L.V. Right and left vagi.

part in the regulation of respiration than do the inspiratory impulses; and one observer (Gad) goes so far as to deny altogether the existence of two kinds of respiratory fibres in the vagus. According to Gad, the vagus, as regards the respiratory centre, is a purely inhibitory nerve. Hence the primary effect of dividing both vagi is an increased inspiratory tone, due to the release of the centre from inhibition. According to this view, the centre, unchecked by any reining impulses, enters upon a career of spendthrift activity. Each inspiratory contraction is maximal, but the centre, exhausted by the effort, has to wait a considerable time before it can accumulate sufficient energy for the next; hence the final result of section of both vagi is deepening and slowing of respiration.

There is no doubt that Gad went too far in denying the existence of inspiratory fibres in the vagus. This is shown by the following experiment of Head. According to Gad's view, collapse of both lungs implies simply a removal of the normal inhibitory impulses

ascending the vagi, and is therefore equivalent to division of these two nerves. If, in the rabbit, the left vagus be divided, a tube can be introduced into the left bronchus, and artificial respiration can be performed by alternate inflation and collapse of the left lung, without in any way affecting the respiratory centre, all connections with the latter being destroyed (*v.* Fig. 494). Meanwhile, the animal carries out normal respiratory movements, which can be recorded by the diaphragm slip method. While the slip is contracting regularly, the right pleura is opened and the right lung allowed to collapse. The effect of this collapse, carried up by the right vagus to the centre, is an extreme contraction of the diaphragm, and since the onset of asphyxia is prevented by the artificial respiration carried out on the left lung, the tonic standstill of the diaphragm may last over a minute. In this case, therefore, the effect of collapse of one lung is enormously greater than that produced by section of both vagi, showing that the effect is due, not to abolition of the ordinary inhibitory stimuli, but to excitation of special inspiratory fibres in the vagus by the collapse of the lung.

By means of the string galvanometer, it is possible to show definitely that a collapse of the lungs does set up a nervous impulse travelling up the vagus nerves. This impulse must be inspiratory in character, so that there is no reason to deny the existence of both



FIG. 495. Effect of 10.6 per cent. CO_2 in a Mixture containing 23.3 per cent. O_2 on a Rabbit with both Vagi divided. (F. H. SCOTT.)

The gas was administered between the arrows. Zero line of blood pressure is 32 mm. below bottom of tracing. Compare this figure with Fig. 486, p. 874.

kinds of fibres in these nerves. The effect of electrical stimulation, especially with an ascending constant current, is also strong evidence in the same direction.

According to Lumsden there are two types of afferent fibres in the vagus which affect the respiratory movements:

(a) The impulses travelling up the vagi which quicken the respiratory movements and are concerned in maintaining the normal rhythm he regards as set up not by the lung movements, but by the passage of the air through the trachea and bronchi. Blowing downwards through the upper part of the trachea causes expiration, while a current of air upwards causes inspiration, the impulses being set up by the stimulation of the mucous membranes.

(b) *Extreme expansion*, or extreme collapse of the lungs, also sets up vagal impulses, the reflex effect of which is to tend to bring the lungs to a state of moderate distension. Thus there are really four sets of fibres, two being excited by the passage of air through the trachea, while the other two only come into play under conditions of extreme changes in the volume of the lungs.

After division of both vagi, the total pulmonary ventilation does not, as a rule, undergo any marked changes, and in the absence of anæsthesia the aeration of the blood may be carried out almost, if not quite, as well as in the intact animal. The importance of the vagus action for the organism is shown, however, if we put an increased strain on the respiratory mechanism, as, for instance, by increasing the percentage of carbon dioxide in the air breathed. In the intact animal, this procedure leads first to increased depth, and later to increased frequency of respiration, the total ventilation being thereby augmented to such an extent as to keep the alveolar tension of carbon dioxide almost constant. If the same percentage of carbon dioxide be administered to a chloralised rabbit after section of both vagi, the effect is deepening of respiration but not quickening (Fig. 495). Each inspiratory

movement, however, is already considerable, so that the margin by which increase of pulmonary ventilation is possible, by increase of depth of respiration alone, is not so great as in a normal animal. Moreover, since no quickening of respiration takes place, the increased ventilation rapidly becomes inadequate for the maintenance of the normal alveolar carbon dioxide tension. In the following Table the total amounts of pulmonary ventilation, obtained on administration of mixtures containing carbon dioxide to a rabbit before and after section of the vagi, are compared.

RABBIT, 3 KILOS.			
	Respirations per minute	Vol. of each respiration	Total ventilation per minute
Respiration with air	72	c.c. 19	1368
" 4.2 per cent. CO ₂	96	25	2400
" 8.6 per cent. CO ₂	97	29	2813
" air	72	20	1440
VAGI DIVIDED			
Respiration with air	45	29	1305
" 4.2 per cent. CO ₂	45	34	1530
" 8.6 per cent. CO ₂	42	38	1596

In the decerebrate animal, administration of CO₂ may cause quickening, even after section of both vagi, but it is probable that the adaptation to the changed conditions would not be so perfect as in the animal with vagi intact.

Whether we assume that the prevailing impulses travelling up the vagi are purely inhibitory, or are both inhibitory and augmentor, the resultant effect, by reining in the activity of the centre, is to economise its energy and the energy of the respiratory muscles. The result of the vagal impulses will therefore be to increase the excitability of the respiratory centre and make it more susceptible to slight changes in the carbon dioxide tension of the blood, while maintaining a sufficient margin of energy to meet the increased needs thrown on the respiratory mechanism by augmented metabolism, such as occurs in violent muscular exercise.

APNŒA. If artificial respiration be maintained in an animal, or if, in man, the respiratory movement be forced, so as to produce a somewhat greater ventilation than is effected by the normal respiratory movements, a standstill of respiration is brought about. This condition is called apnœa. This standstill cannot be due to over-oxygenation of the blood, because this is normally practically saturated with oxygen, and further, because a short apnœa can even be produced by excessive artificial ventilation with inert gases, such as hydrogen and nitrogen. It is due to the fact that forced ventilation of the lungs, with air or any inert gases, will reduce the carbon dioxide tension in the blood circulating round the pulmonary alveoli, and therefore round the respiratory centre. A respiratory pause will thus ensue, and will last until the increasing accumulation of carbon dioxide in the blood raises its tension to the normal height at which the respiratory centre is 'set,' so to speak, to respond. If the carbon dioxide content of inspired air be increased to about 4.5 per cent., it is impossible to produce an apnœic

pause, however rapidly the respiratory movements be carried out. It would seem, therefore, that ordinary apnœa is entirely due to deficiency of carbon dioxide tension in the respiratory centre ('acapnia'). It has been suggested that the vagal reflexes engendered by a series of rapid and large inspirations might summate to produce a prolonged inhibition of respiration, but this has not been substantiated by experiment. The chief use of the vagi in respiration seems to be for maintaining, by frequent but short-lasting inhibitions, the excitability of the respiratory centre at a maximum.

Stoppage of respiration is sometimes caused by stimulation of other nervous or sensory surfaces. Thus, when a duck plunges, there is immediate stoppage of respiration, which may last four or five minutes if the animal remains so long under water. The same stoppage may be produced by pouring water on the beak.

'CHEYNE-STOKES' BREATHING. There is a large amount of carbon dioxide, free or fixed, stored in the blood and tissues, and we may compute the whole body of an adult man to contain some 15 or 20 litres of carbon dioxide. The oxygen store of the body is held almost entirely by the hæmoglobin, and does not exceed 1 litre. Now, forced breathing very rapidly washes out carbon dioxide from the large store, but does not at all increase



FIG. 496. Forced Breathing of Air for two minutes, followed by Apnœa for two minutes, and Periodic ('Cheyne-Stokes') Breathing for about five minutes. (DOUGLAS and HALDANE.)

At A, sample of alveolar air contained O_2 , 11.44 per cent. ; CO_2 , 5.58 per cent. Second sample at B, O_2 , 13.55 per cent. ; CO_2 , 5.57 per cent.

the oxygen store. By continuing forced respiratory movements for a minute or two, the carbon dioxide tension, both in the alveoli and in the blood, may be brought down to a very considerable extent. As a result, there is a prolonged period of apnœa. During this period of cessation of respirations, however, the oxygen is being used up, and the tension of this gas in the blood may fall to such an extent that the respiratory centre is excited by lack of oxygen before the carbon dioxide tension in the alveoli has risen to its normal value. As a result of the excitation by oxygen lack, a few breaths are taken, the carbon dioxide tension is further lowered, and the stimulation due to the oxygen lack disappears. There is thus again a cessation of respiration. These periods of cessation alternate with periods of respiration, so that we get a condition of periodic breathing, which is spoken of as Cheyne-Stokes respiration. During the period of apnœa resulting from forced breathing, the great diminution of oxygen tension in the alveoli is shown by the fact that the subject of the experiment becomes blue, and may indeed lose consciousness. There are, at the same time, rhythmic changes in the blood pressure, which rises towards the ends of the periods of the apnœa, falling during the periods of respiration. The first respiration after excessive forced breathing is due to oxygen lack. The period of apnœa may therefore be considerably prolonged, if the onset of oxygen lack be postponed by increasing the tension of this gas in the alveoli at the commencement of the apnœic period. By forcibly breathing

for a period of two minutes in an atmosphere of oxygen, men have succeeded in holding their breath for as long a period as eight minutes (Vernon).

'Cheyne-Stokes' breathing is almost invariably observed as one of the effects of exposure to high altitudes, and is then especially marked during sleep. It is often present when the activity of the respiratory centre is depressed, as in cases of uræmia or pernicious anæmia. Under these circumstances, it may be temporarily removed by administering either oxygen or carbon dioxide (in small percentage) to the patient. The oxygen improves the condition of the centre; the carbon dioxide acts as an added stimulus and rouses its activity.

THE EFFECTS ON RESPIRATION OF CHANGES IN THE AIR BREATHED

We have already seen that a moderate increase in the carbon dioxide percentage of the air breathed (*e.g.* up to 4 per cent.) causes a proportional increase in the ventilation of the lungs and that this is due to the increase of CO_2 and not to the slight diminution in oxygen content. If the amount of carbon dioxide be increased to 12 or 15 per cent., spasm of the glottis is produced by the irritant effects of the carbon dioxide. If these high percentages be administered to an animal by a tracheal tube, violent dyspnœa is produced, which gradually diminishes, and the animal passes into a condition of narcosis, in which the respiratory movements become less, and the oxygenation of the blood is ineffectively carried out, even in the presence of excess of oxygen. The administration of larger percentages, such as 30 or 40 per cent., causes failure of the circulation and respiration, and rapid death, often preceded by convulsions.

CHANGES IN OXYGEN TENSION. Oxygen itself exercises no effects on the respiratory movements. At the normal atmospheric pressure, the tension of oxygen in the alveoli, when air is breathed, is amply sufficient to saturate the hæmoglobin passing through the lungs. Hence no alteration in respiration will be produced by increasing the tension of oxygen in the air breathed above its normal amount.

This statement is true only for the healthy individual. If from failure of the heart and circulation, from diminished oxygen tension, or from severe loss of blood, the oxygenation of the blood is insufficient, marked amelioration of the symptoms may be produced by inhalation of pure oxygen. Especially is this noticeable where there is failure of the heart. In these cases, the heart, already affected, is unable to keep up an adequate circulation and to supply itself with sufficient oxygen. A vicious circle is thus established, in which the heart tends to get steadily worse. By administration of oxygen, an adequate supply of this gas to the heart muscle is assured; the heart beat therefore becomes more effective and the whole circulation is improved.

If a warm-blooded animal be placed in a chamber containing pure oxygen at a pressure of four atmospheres, or air at twenty atmospheres, it dies as rapidly as if it were in an atmosphere of pure nitrogen. At this pressure, the oxidative processes of the body and the intake of oxygen into the lungs are said to be abolished. It is interesting to note that certain other oxidative phenomena, *e.g.* the spontaneous oxidation of phosphorus, also cease if the tension of the oxygen be sufficiently high. Exposure of an animal over a considerable period of time to a pressure of oxygen of two atmospheres may, as Haldane and Lorrain Smith have shown, set up severe inflammation of the lungs and thereby cause death indirectly.

We have seen that the oxygen pressure in the air may be lowered to about 13 per cent. without pronounced discomfort, though there may be blueness of the lips and nails, owing to deficient oxygenation of the blood. With further reduction, hyperpnœa occurs, and, if the administration of low percentages of oxygen, *e.g.* about 10 to 12 per cent. of an atmosphere, be

continued for some time, the subject of the experiment may suffer considerable discomfort. The signs of oxygen lack are severe headache, confusion of thought, vomiting or nausea and a feeling of discomfort in the precordial region. Many experiments have been made, both on animals and on man, by submitting them to a lowered atmospheric pressure in chambers specially built for the purpose. The limit to which the pressure may be reduced varies in different individuals, the variations being determined by the type of respiratory movement of the individual in question, since on the depth of respiration depends the relation between the tension of oxygen in the alveoli and that in the inspired air. The lowest limit at which life is possible corresponds to an oxygen tension in the alveoli of 27 to 30 mm. Hg.

MOUNTAIN SICKNESS. The phenomena just described are exactly similar to those which are regarded as characteristic of mountain sickness. The following Table shows the diminution in the atmospheric pressure at varying heights above the level of the sea :

Height above sea level, in metres	Barometer mm. Hg.	Per cent. of an atmosphere
0	760	100
1000	670	88
2000	593	78
3000	524	69
4000	463	61
5000	410	54
6000	357	47
7000	320	42

At a height of 5000 metres the pressure of the air is reduced to little over half an atmosphere, and the oxygen tension is therefore only about 11 per cent. of an atmosphere. It must be remembered that in most cases of mountain sickness, in addition to this absolute oxygen lack, there is increased consumption of oxygen, owing to the muscular exercise involved in climbing. Moreover a greater *volume* of the alveolar air must consist of carbon dioxide if the *tension* of this gas is to be kept constant (cp. Fig. 487, p. 875). Since diminished oxygen tension, within fairly wide limits, does not excite any corresponding increase in the respiratory movements, there must, at these heights, be an actual diminution in the oxygen tension in the alveoli. This diminution in tension is shown by a series of observations carried out by Zuntz, on himself and fellow-workers, at different localities. It may be noted that on Monte Rosa, where the oxygen tension in the alveoli was reduced to between 37 and 57 mm. Hg, as against the normal 101 to 107 mm. Hg, all the members of the party were suffering from mountain sickness.

	Height above sea level, in metres	O ₂ tension of air, mm. Hg.	Alveolar O ₂ tension, mm. Hg.					
			A	B	C	D	E	F
Berlin	54	157	105	101	—	105	103	104
Brienz	500	148	84.5	94	80	88	86	91
Brienzer Rothorn	2130	121	68	66	64	62	66	71
Col d'Olen	2900	110	57	—	—	60	68	68
Monte Rosa	4560	89	—	46	49	51	37	57

As a result of the oxygen starvation, there is inadequate supply of this gas to the heart, so that the circulation tends to fail, especially on making the slightest muscular movements. At the same time, the oxygen starvation of the brain produces failure of judgment and inability to carry out or to co-ordinate muscular movements properly. The symptoms, as a rule, do not become worse until just before death, so that, although there is an oxygen starvation of the body, there must be some means by which the respiration is modified so as to obtain a sufficiency of this gas for the lowered requirements of the body. That the adaptation is effective, is shown by the fact that most individuals, if they remain at a height, gradually recover from the mountain sickness and may finally be able to carry out muscular movements with almost as great precision and force as they could previously on the plains. Increased ventilation of the lungs is attained because of the effect of oxygen lack upon the centre. If the oxygen lack is very acute, there may also be production of acid substances in the body. Since the carbon dioxide is no longer the sole factor responsible for the ventilation, the tension of this gas in the alveolar air is diminished, sometimes so much that the blood at first becomes definitely more alkaline, and the hyperpnœa is maintained chiefly through the oxygen lack.

This mechanism, however, affords only a means of immediate adaptation, and is not operative in the adaptation which comes on gradually during residence at a high altitude. Part of this adaptation appears to depend upon the excretion, by the kidneys, of bicarbonate from the blood, thus compensating for the low content of free CO_2 . Under these conditions, as Barcroft has shown, the reaction of the blood is practically normal, as shown by the colorimetric method, as well as by the ratio of the free to the combined CO_2 in the whole blood.

Another important means of rapid adaptation is by means of the circulation. This is noticeable even in the case of persons sitting quietly in a chamber subjected to gradually lowered pressures. It is evident that a deficient oxygenation of the blood may, so far as the tissues and heart are concerned, be compensated by increasing the rapidity of the circulation; and this is effected. The following Table shows the changes in the pulse rate caused by exposure to varying pressures in a gas chamber:

PULSE IN CHAMBER AT REDUCED PRESSURES.

Pressure									Pulse
720	.	.	.	.	.	.	.	.	64
650	.	.	.	.	.	.	.	.	72
424	.	.	.	.	.	.	.	.	84

This quickening of the pulse is to be observed also in the trained mountain soldier, and in individuals in whom there is no lowering of the alveolar carbon dioxide tension, so that apparently, in such cases, the whole adaptation to altered conditions is by means of the circulation. In cases where adaptation fails, it is in the circulation that the failure is most marked, so that the symptoms of severe mountain sickness closely resemble those produced by heart failure. The disturbance of the central nervous system is shown by the almost invariable occurrence of Cheyne-Stokes breathing at great heights. But this mechanism, again, is only immediate and does not explain acclimatisation to life in mountain districts. Barcroft, in the Peruvian Andes (4,400 metres) found that at rest the pulse was normal and that there was no increase in the circulation rate.

But if the animal is able to withstand the immediate effects of exposure to a rarefied atmosphere, a process of adaptation comes into play which finally

fits him for discharging his functions normally, even at the high altitude. The change in the oxygen saturation of the blood is at once felt by the blood-forming organs. As an immediate effect of change to a region of low atmospheric pressure, there is a relative increase in the blood corpuscles, due to a concentration of the blood and a diminution of its plasma, and perhaps also to a contraction of the spleen. Simultaneously, however, the blood-forming organs enter into a condition of increased activity, so that, after a stay of four or five weeks' duration at a height, both corpuscles and hæmoglobin are considerably increased in total amount. The following Table shows the average number of red corpuscles contained in one cubic millimetre of blood from the inhabitants of regions at varying altitudes :

	Height above sea level, in metres	Red corpuscles
Christiania . .	0	4,970,000
Zurich . . .	412	5,752,000
Davos . . .	1560	6,551,000
Arosa . . .	1800	7,000,000
Cordilleras . .	4392	8,000,000

We are probably here making use of an adaptation which has been evolved for the purpose of retrieving loss of blood by hæmorrhage, such as must have been of continued occurrence in the struggle which has resulted in the survival of the animals of to-day.

At the same time, there is a rise in the excitability of the respiratory centre and the total ventilation is increased, so that the alveolar oxygen tension is raised 10 or 12 per cent. above that which it would otherwise possess.

There is, of course, a limit to the power of adaptation, a limit which varies in different individuals. Thus, for some men, it is impossible to stay any length of time in the high settlements in the Andes, while others, after two or three weeks' discomfort, become perfectly inured to their new conditions. It seems doubtful, however, whether any of the present race of men could become adapted to permanent residence at a height over 6000 metres, though for a certain length of time, by bringing into play the reserve mechanisms already described, they may raise themselves to a height considerably above 7000 metres. The highest summits in the Himalayas have a height approaching that attained in 1875 by Tissandier with his two companions in his famous balloon ascent, namely, 8600 metres. In this ascent, although oxygen inhalation was used (somewhat ineffectively), two of the party succumbed. The expeditions to Mount Everest showed, however, that when acclimatisation was gradual, men could live at about the same altitude, without oxygen inhalation. But at such heights, the slightest exertion, *e.g.*, changing from lying to sitting, caused extreme breathlessness.

The stimulating effect of oxygen lack on the blood-forming organs extends also to the muscular system, so that one of the effects of a residence in high altitudes is increased assimilation of nitrogen from the diet. For a time, the nitrogen output is less than the nitrogen intake, and there is an actual building up of new tissue, no doubt mainly muscle.

ALTERATIONS IN THE NITROGEN TENSION. The nitrogen of the atmosphere must be regarded as a purely inert gas. It is a matter of indifference whether, under normal atmospheric pressure, we breathe an

atmosphere of pure oxygen, or one containing one-fifth part of this gas diluted with four-fifths of nitrogen. The very inertness of nitrogen may be of danger to the body under certain conditions. If a man or an animal be exposed, as in a diving-bell, to a pressure of three to six atmospheres, the respiratory functions are unaffected, but the small amount of nitrogen dissolved in the fluids and adipose tissue of the body is increased in direct proportion to the pressure. If the pressure be now suddenly released, the nitrogen, which cannot be used up by the tissues, is given off from the body fluids in the form of highly insoluble bubbles. These bubbles, occurring in all the capillaries, obstruct the flow of blood, and therefore, if the evolution of gas is sufficiently large, the animal dies in convulsions. A similar evolution of gas may occur in the spinal cord, causing destruction of the cord and paralysis ('caisson disease'; 'divers' palsy'). In order to prevent this sudden evolution of gas, it is necessary that the change from the high pressure to the ordinary atmospheric pressure should be carried out gradually, so as to give the tissues time to get rid of their excess of nitrogen without the formation of bubbles.

OTHER GASES. Hydrogen and methane are, like nitrogen, indifferent gases. They may be used, instead of nitrogen, to dilute the oxygen that we breathe, without harm or inconvenience.

Carbon monoxide is rapidly poisonous by its action on the red corpuscles. It combines with hæmoglobin, forming CO-hæmoglobin. The blood is therefore deprived of its oxygen carrier, and the animal dies of asphyxia. But, although the avidity of CO for hæmoglobin is about 300 times that of oxygen, we can convert the CO-hæmoglobin back into oxyhæmoglobin by increasing the mass influence of the oxygen and by adding CO₂. This may be done by giving the poisoned animal pure oxygen to breathe, or, better, oxygen containing 5 per cent. CO₂.

The curve relating CO-saturation to CO-pressures is similar in form to the oxygen dissociation curve, but, as shown by Douglas, Haldane and Haldane, the CO-pressures required are very small, only about $\frac{1}{245}$ th as great as the oxygen pressures. Thus, we get half saturation of the blood with CO at a CO-pressure of about 0.13 mm. Hg (in presence of 40 mm. CO₂), whereas for oxygen we require a pressure of about 32 mm. (with 40 mm. CO₂). When, however, oxygen and carbon monoxide are both present, the saturating power of carbon monoxide is not 245, but 310, times as great as oxygen. This is possibly due to the fact that the velocity constant for oxygenation of hæmoglobin is about 7.5 times as great as that for reduction, together with the fact that, although the rate of combination of CO with hæmoglobin is only one-tenth as great as for oxygen, the rate of dissociation of CO-Hb is only $\frac{1}{2450}$ of that of HbO₂. Hence the stability of CO-Hb is due, not to the speed of its formation, but to the slowness of its dissociation. (Hartridge and Roughton.)

Other gases which have specially poisonous properties are hydrocyanic acid, sulphuretted hydrogen, phosphuretted hydrogen (PH₃), arseniuretted hydrogen, etc.

IRRESPIRABLE GASES are those which are so irritating that they produce spasm of the glottis. Such are ammonia, chlorine, sulphur dioxide, nitric oxide and many others.

VENTILATION

A point of practical importance is the securing to each individual of sufficient fresh air. It is found that a dwelling-room becomes unpleasant and stuffy when the amount of CO₂ present has reached 0.1 per cent. This stuffiness is supposed to be due to organic exhalations from the skin, lungs and alimentary canal, some of which have a poisonous effect, giving rise to headache and sleepiness. As these cannot be measured, it is taken as a

cardinal rule in ventilation that the amount of CO_2 should never rise above 0.1 per cent.

Since in questions of ventilation we have generally to deal with trades in which the metric measure is not used, it may be convenient to give in cubic feet the data as to carbon dioxide production and the amount of air required.

An adult man gives off about 0.6 cubic foot of CO_2 every hour. Hence, in that time he raises the amount of CO_2 in 1000 cubic feet of air from 0.04 per cent. (the normal amount in the atmosphere) to 0.1 per cent. He must, therefore, be supplied with 2000 cubic feet of air per hour, in order to keep the amount of CO_2 down to 0.07 per cent.

(Ordinary air contains 0.04 per cent. CO_2 , therefore 2000 cubic feet would contain 0.8 cubic foot CO_2 , which with the 0.6 cubic foot given off by the man would be 1.4, which is 0.07 per cent.)

In order that the air may be easily renewed without giving rise to excessive draught, a certain amount of cubic space must be allotted to each man. Each adult in a room should have 1000 cubic feet of space, and be supplied every hour with 2000 to 3000 cubic feet of air.

✓ CHAPTER XL

RENAL EXCRETION

THE COMPOSITION AND CHARACTERS OF THE URINE

WATER, taken as such with the food, but also derived to a slight extent from the oxidation of hydrogen, is got rid of by the lungs, skin, and kidneys. The salts of heavy metals, *e.g.* iron, bismuth, mercury, when administered, are excreted for the most part by the alimentary canal. The residues of the bile and digestive secretions are also eliminated with the fæces. With these exceptions, practically all the waste products resulting from metabolism are excreted in the urine by the kidneys. We have thus in this fluid the last chapter in the metabolic history of a large number of the constituents of the body. Since, moreover, the kidneys may excrete almost any substance which circulates through their blood vessels, many of the intermediate metabolites may be found in minute quantities in the urine and may be isolated by working up large quantities of this fluid. Under pathological conditions, these metabolites may appear in the urine in larger amounts and serve then as an index to some interference with metabolism.

The composition of the urine must, therefore, be a variable one, according to the activity of the body, the quantity and nature of the food taken, and the relative amount of water escaping by the kidneys, lungs, and skin respectively. But we can describe an average composition for the urine. The history of the urinary constituents has been given for the most part in the chapter dealing with metabolism, but we will enumerate in this chapter the various constituents of the urine and summarise their properties and normal significance.

The urine of man is a clear yellow fluid, which froths when shaken. On standing, a cloud of mucus is deposited, consisting of a very small amount of nucleoprotein derived from the epithelial lining of the bladder and urinary passages. In concentrated urine a deposit occurs on cooling. This deposit dissolves when the urine is warmed, and consists of *urates*. When normal urine is turbid as it is passed, the turbidity generally consists of earthy phosphates and is not cleared up by heating.

The *colour* of the urine varies with its concentration. After severe sweating the amount of water excreted by the kidneys is small, and the urine is therefore of high colour. After copious draughts of liquid the urine may be very pale.

Ordinary urine has an aromatic *odour*, but this varies largely with the character of the food.

The *specific gravity* and the *molecular concentration* of the urine is proportional to its concentration. Normally it is 1016 to 1020, though it may rise as high as 1040 or sink as low as 1002.

Its osmotic pressure is usually much above that of the blood plasma. Thus, the Δ of urine normally varies between 0.87 and 2.71° C. (Δ of blood =

0.56°). After copious draughts of water the depression of freezing-point of the urine may be less than that of serum, and may be as small as 0.25° C.

The *reaction* of urine is generally acid. This is due to the fact that neutral constituents of the food may give rise to acid end-products in metabolism. The sulphur of proteins is converted into sulphuric acid and the phosphorus of lecithin into phosphoric acid. There is thus a predominance of acid radicals over bases in ordinary urine. The pH of the urine can easily be determined by indicators, and is on the average 5.3, and varies from 6.5 to 5.0. This statement, however, applies only to man and to carnivora. In the food of herbivora there is a predominance of alkaline bases. Vegetable acids, *e.g.* tartaric, malic, and citric acids, undergo oxidation in the body, so that their bases leave the body as alkaline carbonates. The urine of such animals therefore contains an excess of alkaline carbonates, and is alkaline in reaction and turbid. If a herbivorous animal be starved so that it has to live on its own tissues, its urine becomes clear and acid. The urine of man can be made alkaline by the ingestion of large quantities of vegetables, by the administration of alkalis (*e.g.* NaHCO_3) by the mouth, or by prolonged forced breathing. Under such circumstances, the urine, as passed, is generally turbid from the presence of precipitated earthy phosphates. In determining the titratable acid of the urine, it is usual to adhere to one indicator, *e.g.* phenolphthalein, and to give the acidity in terms of decinormal acid, naming the indicator used.

Owing to the buffering action of phosphates, the *titratable acidity* of urine is always much greater than the H-ion concentration would suggest. By titrating, first with methyl orange and an acid, and then with phenolphthalein and an alkali, we obtain a useful measure of the buffers of the urine. By the first titration we convert the dibasic phosphates to the monobasic salt (NaH_2PO_4), and by the second we convert the monobasic to the dibasic phosphate (Na_2HPO_4). Hence the ratio of the first to the second titration gives us the ratio $\frac{\text{Na}_2\text{HPO}_4}{\text{NaH}_2\text{PO}_4}$. (Leathes).

THE AVERAGE COMPOSITION OF THE URINE. The following may be taken as a fair daily average for an adult man on ordinary mixed diet :

Total amount of urine = 1500 c.c.

This contains about 60 grammes of solids, of which 25 grammes are inorganic and 35 grammes organic. They are distributed as follows :

INORGANIC CONSTITUENTS		ORGANIC CONSTITUENTS	
Sodium chloride	15.0 grammes	Urea	30.0 grammes.
Potassium	3.3 "	Creatinine	1.0 "
Sulphuric acid	2.5 "	Uric acid	0.7 "
Phosphoric acid	2.5 "	Hippuric acid	0.7 "
Ammonia	0.7 "	Other substances	2.6 "
Magnesium	0.5 "		
Calcium	0.3 "		
Other substances	0.2 "		

The quantity of urine will naturally vary with the water leaving the body by the kidneys, and, therefore, according to the habit of the individual with regard to the intake of fluids and with his occupation. Thus, after copious sweating, the total amount may fall to 400 c.c. in the course of the day. If large draughts of liquid be taken, it may rise to 3000 c.c. or more. There are also diurnal variations in the amount secreted, probably depending largely on the circulation through the kidneys. The secretion is at a minimum during sleep, and especially between 2 and 4 o'clock in the morning. It is at its maximum during the first hours

after rising, and increases generally after each meal. Muscular exercise may also give an initial increase, owing to the greater vigour of the circulation associated with exercise. If the exercise is severe enough to cause sweating, or is carried to fatigue, there may be a consequent diminution in the amount of urine secreted.

THE INORGANIC CONSTITUENTS OF THE URINE

(a) ACID RADICALS. The *chlorides* of the urine are derived almost entirely from the chlorides of the food. The output of chlorides, which normally varies from 6 to 10 grammes Cl. in the course of the day, will therefore depend on the amount of chlorides taken in with the food. If these be withdrawn altogether, the chlorides may almost disappear from the urine, although the circulating blood contains practically the same amount of chlorides as in the normal individual, showing that the body retains as long as possible, the chlorides necessary for the proper carrying out of the vital processes. Chlorides may also temporarily disappear from the urine under various pathological conditions, *e.g.* acute pneumonia.

Sulphates. The sulphates of the urine are derived almost entirely from the oxidation of the sulphur of the protein molecule. Hence, as the nitrogen of the urine goes up, so the sulphates will increase. On an average diet, the ratio of urinary nitrogen to SO_3 is about 5 : 1; though this ratio will alter with the nature of the protein taken as food. The daily output of sulphuric acid varies between 1.5 and 3 grammes SO_3 . The greater part of the sulphate is present as sulphates of the alkaline metals. A certain proportion, about 10 per cent., occurs in the form of conjugated or ethereal sulphates, chiefly indoxyl sulphate. A small proportion of the sulphur excreted in the urine is in unoxidised form as so-called neutral sulphur. The neutral sulphur probably includes a number of different bodies, among which thiocyanates and cystine are the best known.

Phosphates. The phosphates of the urine are derived, partly from the phosphates of the food, partly from the oxidation of the organic phosphorus-containing constituents of the food and of the tissues, *e.g.* nuclein, lecithin, &c. If the food contains much calcium and magnesium, the amount of phosphates excreted in the urine diminishes, since these substances are excreted with the fæces as calcium and magnesium phosphates. According to the diet therefore, phosphoric acid may be excreted either by the intestine or by the kidneys. The amount of phosphates, reckoned as P_2O_5 , excreted in the course of the day may vary between 1 and 5 grammes. In the urine, the phosphates exist as a mixture of the mono- and di-sodium phosphates, the relative amounts of the two being the chief factor in determining the acidity of the urine. If the urine is neutral or alkaline there is very often a deposit of earthy phosphates. Whether this deposit is present or not, depends on the varying solubility of the different calcium and magnesium phosphates. Thus the mono-magnesium phosphate $\text{MgH}_4(\text{PO}_4)_2$ and the mono-calcium phosphate $\text{CaH}_4(\text{PO}_4)_2$ are both fairly soluble in water, and their solubility is increased by the presence of neutral salts. With lowered acidity of the urine, the proportion of the two bases present in these forms is diminished. The di-magnesium and di-calcium phosphates are only slightly soluble in water, and the latter would, if present in the urine, be deposited. One may indeed, in slightly acid urine, find the di-calcium phosphate occasionally present as a crystalline deposit ("stellar phosphate"). On heating the urine, the di-calcium phosphate breaks up into a mono-calcium phosphate and a

tri-calcium phosphate, while the acidity of the urine is increased by the solution of the mono-calcium phosphate. Alkaline urine will always present a precipitate of tri-calcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$. When normal urine is allowed to stand, the urea is converted by the presence of micro-organisms into ammonium carbonate, and the urine become alkaline. Under such conditions we may often find a crystalline precipitate of ammonium magnesium phosphate, NH_4MgPO_4 , the so-called 'triple phosphate.'

(b) THE BASES OF THE URINE. The bases include potassium, sodium, ammonium, magnesium and calcium.

The amount of *potassium* excreted in twenty-four hours varies between 1.9 and 3.2 grammes, according to the nature of the food taken. With a large meat diet the output of this base is increased. In fasting it also increases, owing to the utilisation of the tissues of the body, which themselves are rich in potassium.

The amount of *sodium* excreted in the twenty-four hours is on the average about 5 grammes, but fluctuates largely with the diet.

Calcium and *magnesium* are invariably present in urine, but in much smaller quantities than the alkaline metals. The average amount of these two bases in the twenty-four hours varies in each case between 0.1 and 0.2 gramme. Their output by the urine is no criterion of the amount taken in with the food, or absorbed from the intestines, since both these bases may be re-excreted into the gut and appear as insoluble phosphates in the fæces.

Normal human urine always contains a small amount of *ammonia*, on an average between 0.6 and 0.8 gramme in the twenty-four hours. As we have already seen, in dealing with the origin of urea in the body, the quantity of ammonia in the urine is an index to the excess of acids over bases which have to be excreted by this fluid. According to Nash and Benedict, the ammonia of the urine is almost entirely formed in the kidney itself, from amino acids or urea, and does not represent an excretion from the blood, in which it is only present to the extent of 0.1 m.g. per 100 cc. The experiments of Bliss, however, throw some doubt on this, and suggest that ammonia can be, and is, formed in all the tissues, including the kidney.

It is usual to reckon *iron* among the bases which may be excreted by the urine. The amount of this substance in the urine is extremely small, as a rule less than 5 milligrammes in the day, since the main channel of excretion of this substance is the intestine.

ORGANIC CONSTITUENTS OF THE URINE

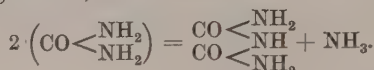
Almost all these constituents contain nitrogen, which in man on an ordinary mixed diet is distributed among the various urinary constituents as follows :

Urea	.	.	.	.	.	85-90 per cent.
Ammonia	.	.	.	.	.	2-4 "
Creatinine	.	.	.	.	.	3 "
Uric acid	.	.	.	.	.	1-3 "

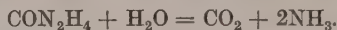
About 6 per cent. of the urinary nitrogen is in the form of other substances, such as hippuric acid, pigments, &c. All the organic constituents of the urine (except hippuric acid) are obtained direct from the blood; hence they represent real excretory products. Their origin in the body has already been discussed in Chapter XXX.

UREA, $\text{CO} \begin{array}{c} \text{NH}_2 \\ \diagup \quad \diagdown \\ \text{NH}_2 \end{array}$ or $\text{NH} : \text{C} \begin{array}{c} \text{NH}_2 \\ | \\ \text{O} \end{array}$, may be obtained in long, anhydrous,

colourless prisms. It is soluble in water and alcohol, and insoluble in ether. Its solutions are neutral in reaction, but it forms crystalline salts with strong acids. Some of these salts, *e.g.* the nitrate and oxalate, are almost insoluble, and have a characteristic crystalline form. Urea, when heated, melts at about 130° C. On further heating it undergoes decomposition, giving off ammonia and forming biuret, as follows :



At the same time, a certain amount of cyanic acid is formed, and this polymerises to cyanuric acid, $\text{H}_3\text{C}_3\text{N}_3\text{O}_3$. On heating with alkalis or with strong acids, urea undergoes hydrolysis, with the production of carbon dioxide and ammonia :



The same change is effected in urea by certain micro-organisms, *e.g.* the *micrococcus ureæ*, which is responsible for the ammoniacal change which occurs in urine when exposed to the air. This action is due to an enzyme, *urease*, which is also present in certain plant tissues, *e.g.* the seeds of the soya bean and jack bean. When urea, in slightly acid solution, is incubated with ground soya bean, the urea is all converted into ammonium salts ; on making the fluid alkaline the ammonia is liberated and may be removed by a current of air and absorbed in a standard acid. This forms the basis of a method for the estimation of urea.

Urea solutions when mixed with alkaline hypobromite solutions evolve nitrogen :—



The CO_2 formed is absorbed by the excess of caustic alkali, and if the evolved nitrogen be measured an approximate estimate of the urea is obtained.

Another test and method for estimation of urea is based on the fact that when a solution of urea, acidified with acetic acid, is mixed with a solution

of xanthydrol $\left(\text{C}_6\text{H}_4 \begin{array}{c} \text{CHOH} \\ \diagup \quad \diagdown \\ \text{O} \end{array} \text{C}_6\text{H}_4 \right)$ in methyl alcohol, a white insoluble

precipitate is formed, which contains exactly one-seventh of its weight of urea.

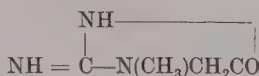
Urea, being the chief nitrogenous constituent of the urine, is the most important index to the protein metabolism of the body. It may be regarded as partly exogenous, partly endogenous. The greater part of the 30 grammes excreted by a normal individual in the course of the day is exogenous, and we have already seen that it is formed in the liver (Chapter XXX.).

Urea may easily be prepared from urine by evaporating to dryness with animal charcoal and extracting the dry residue with acetone. On evaporation of the filtered extract, urea crystallises out.

CREATININE. Creatinine is a normal constituent of urine, in which it occurs in quantities of 0.8 to 1.3 grammes in the twenty-four hours. It is easily produced from creatine by boiling the latter with strong hydrochloric acid, when a process of dehydration occurs. Creatine has the formula :



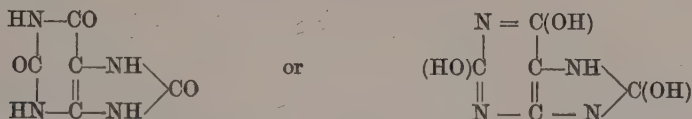
On dehydration it is converted into creatinine :



(1) **WEYL'S TEST.** On treating a solution of creatinine with a small quantity of very dilute sodium nitroprusside solution and then with weak caustic alkali, a rich ruby red colour is produced, which gradually changes to yellow. On now adding acetic acid, and warming, the solution becomes green and then blue, and finally a precipitate of Prussian blue is formed.

(2) **JAFFE'S TEST.** On treating a solution of creatinine with a few drops of a watery solution of picric acid and dilute caustic potash, an intense red colour is produced. This reaction is made use of for the quantitative estimation of creatinine in the urine.

URIC ACID. Uric acid is 2-6-8-trioxypurine.



Uric acid forms small rhombic crystals. The crystalline form varies considerably in the presence of impurities. The different forms of uric acid crystal which may occur in the urine are shown in Fig. 497. It is extremely insoluble in pure water, one part of uric acid requiring 39,000 parts of water at 18° C. for its solution. It is easily soluble in concentrated sulphuric acid and in alkalis. The amount of uric acid per day varies, according to the diet, from 0.4 to 1.0 gramme. Uric acid can be prepared from urine by precipitation, as ammonium urate, with excess of ammonium chloride and ammonia. The precipitate is collected and treated with dilute acid, when uric acid crystallises out.

URATES. Uric acid acts as a weak dibasic acid. It forms three orders of salts, namely, the neutral urates, the bi-urates and the quadri-urates. The neutral urates, $\text{M}_2\bar{\text{U}}$, are very unstable, and exist only in the presence of caustic alkalis. The bi-urates, $\text{MH}\bar{\text{U}}$, are the most stable of the urates. They may be prepared by dissolving uric acid with the aid of heat in weak solutions of the alkaline carbonates, from which they separate, on cooling, in stellar crystals.

The quadri-urates have the formula $\text{H}_2\bar{\text{U}}$, $\text{MH}\bar{\text{U}}$. They may be prepared by boiling uric acid with dilute solutions of potassium acetate. On cooling the mixture, the quadri-urate separates as an amorphous precipitate or in crystalline spheres. The quadri-urates are extremely unstable, and in the presence of water are broken up into the bi-urates and free uric acid. It is probable that under normal conditions the greater part of the uric acid in the urine is present in the form of a quadri-urate (Roberts), and the so-called 'lateritious deposit,' the brick-red amorphous precipitate of urates which occurs in concentrated urine on cooling, consists of these quadri-urates. The exact condition of the urate, however, will depend on the reaction of the urine.

When the urine is acid, *i.e.* when there is a predominance of acid phosphates, there will be a tendency to the precipitation of uric acid. If, however, the di-sodium phosphate be in excess, the uric acid may be kept in solution as the quadri-urate, or even as the bi-urate.

Small traces of purine bases also occur in urine, namely xanthine, hypoxanthine and adenine. When tea and coffee are taken the methyl purines may occur, namely, caffeine, theobromine and their derivatives.

HIPPURIC ACID, or benzoyl glycine, is a frequent, though not a constant, constituent of human urine. It is derived from benzoic acid, or from any aromatic substance which, on oxidation, can give rise to benzoic acid. In the kidneys, the benzoic acid is conjugated with glycine to form hippuric acid. The amount of hippuric acid excreted in the day may vary between 0.1 and 1 gramme. After a diet rich in fruit or vegetables its amount

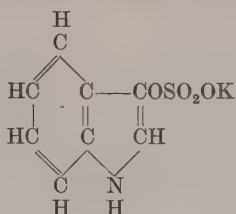
may rise to 2 grammes. It is present in considerable quantities in the urine of herbivora and may be most easily prepared from horses' urine. Hippuric acid has the formula :



It can be obtained in milk-white crystals, which are only slightly soluble in cold water, but easily soluble in alcohol and in ethyl acetate. It is insoluble in petroleum ether and benzol. On heating, it is broken up into benzoic acid and glycine. On heating with concentrated nitric acid, it forms nitro-benzene, which can be recognised by its characteristic smell of bitter almonds.

AMINO-ACIDS. According to Levene and van Slyke, amino-acids are always present in the urine, and contribute about 1.5 per cent. of the total nitrogen.

OTHER AROMATIC SUBSTANCES. The chief of these is the so-called 'urinary indican' or potassium-indoxyl-sulphate. This is derived from the indol produced in the intestines from the tryptophane contained in the proteins of the food, the change being effected by the influence of the micro-organisms of putrefaction. Urinary indican has the formula :



It is converted into indigo by the action of mild oxidising agents (*e.g.* HCl and ferric chloride), and when subsequently shaken with chloroform the chloroform layer is seen to be deep blue.

THE URINARY PIGMENTS. Normal urine gives no definite absorption bands. It owes its colour to the presence of a yellow pigment, *urochrome*. In order to separate urochrome from urine, the urine is saturated with crystals of ammonium sulphate and filtered. The filtrate, which still contains nearly all the colour of the urine, is shaken up with alcohol, which withdraws the greater part of the colouring matter. On concentrating the alcoholic solution and pouring it into an equal volume of ether, an amorphous brown precipitate falls, which is the urochrome. Urochrome, on treatment with aldehyde, yields a pigment closely similar to urobilin. On the other hand, urobilin, treated with potassium permanganate, is converted into a substance practically identical with urochrome. Urochrome may therefore be derived from the same source as urobilin.

According to Roaf, urochrome is, at least in part, derived from the chlorophyll of green plants taken as food.

Urobilin is only present in traces in normal urine, and then chiefly in the form of a chromogen, *urobilinogen*, from which it must be set free by acidification. In certain pathological conditions, especially in cirrhosis of the liver, urobilin may occur in the urine in considerable quantities.

Urobilin in solution gives a single absorption band between the lines *b* and *r*, *i.e.* at the junction of the green and blue of the spectrum. On treatment with zinc chloride and ammonia, its solutions show a well-marked green fluorescence. The urobilin of urine is identical with stercobilin, the colouring

matter of the fæces. It is formed in the intestines by the action of micro-organisms on bile pigment.

Urobilin may be detected in the urine by Schlesinger's test. The urine is acidified with acetic acid and extracted with amyl alcohol. The amyl alcohol layer is removed and a few drops of alcoholic zinc chloride added, when a green fluorescence appears.

Urobilinogen is detected by Ehrlich's test—addition of a solution of *p*-dimethyl-aminoazobenzaldehyde in 50 per cent. HCl gives a red colour.

Other pigments which may occur in urine are uroerythrin and hæmatoporphyrin. *Uroerythrin* gives the pink colour to urate sediments. Its chemical nature is not known. It is distinguished by the fact that on addition of caustic soda the pink colour is changed to green. On suspending the red-coloured precipitate of urates in hot water and extracting with amyl alcohol, a pink solution is obtained which shows two absorption bands in the green part of the spectrum.

Hæmatoporphyrin is present only in very small amounts in normal urine, but under certain conditions, especially after poisoning with sulphonal, it may occur in such large quantities as to give the urine a deep purple colour. Under these circumstances it is found in the form of alkaline hæmatoporphyrin and gives the characteristic absorption bands of the latter.

Urorosein is a name that has been given to a pigment which is formed when the urine is treated with strong mineral acids. It is probably an indol derivative. It gives a single absorption band between the lines D and E.

ABNORMAL CONSTITUENTS OF THE URINE

A very large number of substances occur in minute traces in the urine and may be detected when large quantities of this fluid are worked up at one time. Most of the so-called pathological constituents may be detected in this way in normal urine. It is only when they occur in easily detectable amounts that their presence becomes of any significance.

COAGULABLE PROTEIN. Under normal circumstances, urine is free from protein except the small traces of mucinous material which gives the cloudiness to the urine. If the kidney cells are damaged by disease, by interference with their blood supply or by circulating poisons, the glomerular epithelium permits the passage of a certain amount of the proteins of the plasma. Under these circumstances, after histological fixation, the coagulated protein may be seen in Bowman's capsule. The presence of coagulable protein (generally spoken of as albumin) in the urine is significant of the pathological conditions of the kidney associated with Bright's disease. A small trace will generally be found in the urine which is passed shortly after taking muscular exercise. Under this condition the presence of albumin in the urine has no pathognomonic significance.

The proteins generally found are identical with those of the blood plasma and consist of serum albumin and serum globulin. Their presence in the urine may be detected by the precipitate produced on neutralising and then boiling. In carrying out this test a few cubic centimetres of saturated salt solution should be added and one or two drops of dilute acetic acid. A more delicate test is that known as Heller's. Some strong nitric acid is placed in a test-tube and the urine is poured carefully down the side of the tube so as to form a layer on the surface of the nitric acid. If albumin be present, a white ring is formed at the junction of the two liquids.

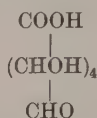
HÆMOGLOBIN is present in the urine when hæmolysis occurs in the blood stream.

SUGAR. In diabetes, the amount of sugar in the blood is increased, and sugar appears in large quantities in the urine. The sugar is practically always glucose. Lactose may occur in the urine of nursing women even in conditions of health.

In renal glycosuria, the kidney allows sugar to pass too readily; hence glucose appears in the urine, but the blood sugar is rather lower than normal.

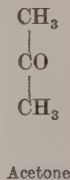
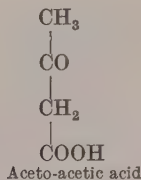
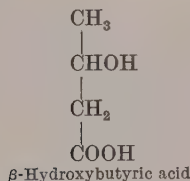
In rare circumstances, fructose or pentose may be found in the urine. The former would be detected by the fact that it rotates polarised light to the left instead of to the right, as is the case with glucose.

GLYCURONIC ACID. Small traces of this are present in normal urine. It occurs as a conjugated acid after the administration of various substances, *e.g.* camphor or chloral. If phenol, indol or skatol be given to an animal which is receiving very little protein in its diet, these substances will leave the body conjugated, not with sulphuric acid, but with glycuronic acid. Glycuronic acid may be regarded as the first product of oxidation of glucose, having the formula :



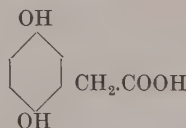
It reduces Fehling's solution and rotates the plane of polarised light to the left.

ACETONE BODIES. These substances often occur associated with glucose, in diabetes, especially towards the end of the disease. They represent the penultimate stages in the oxidation of the fats. Their relation to one another is seen from their formulæ



They may also occur in any condition of carbohydrate starvation, relative or absolute. **CYSTINE.** This substance, which is a normal product of the hydrolysis of proteins, is found as a constant constituent, to the amount of half a gramme a day, in the urine of certain individuals. The condition of cystinuria represents, like alcaptonuria, an inborn error of metabolism, and persists throughout life. In such cases, the cystine may give rise to urinary deposits or even to a urinary calculus.

HOMOGENTISIC ACID. This is an aromatic acid having the composition of dioxyphenyl acetic acid. Its formula is as follows :



It occurs as a constituent of the urine of certain individuals, who are said to be affected with *alcaptonuria*. The urine of these cases is remarkable for its resistance to putrefactive changes. It slowly darkens on exposure to the air, and on the addition of alkali and shaking with air it becomes rapidly brown or black. It reduces Fehling's solution, so that the presence of sugar may be suspected. Such urine contains homogentisic acid in a quantity of 3 to 6 grammes per day. It seems that, in these cases, the power of the organism to break up tyrosine and phenylalanine is entirely absent. If either of these substances be administered by the mouth, it is converted almost quantitatively into homogentisic acid, which appears in the urine. Alcaptonurics apparently suffer no ill effects as a result of their abnormal metabolism.

BILE PIGMENTS. Bilirubin and biliverdin are present in the urine in jaundice, owing to the presence of bilirubin in greatly increased amount in the blood plasma.

BILE SALTS are also often detectable in the urine in obstructive jaundice, *e.g.* in jaundice due to gall-stones.

URINARY DEPOSITS

In addition to formed elements, such as blood corpuscles, bacteria, or pus cells, which may occur in abnormal urine, the following deposits may be found :

(a) *In Acid Urine.* (1) Amorphous urates occur generally as a brick-red amorphous deposit, thrown down as the urine cools. It is redissolved

on warming the urine, and consists generally of the quadri-urates. The acid urate of sodium and of ammonium may occasionally occur in star-shaped clusters of needles or as spherules with small crystals adhering to them.

(2) Uric acid. Whetstone, dumb-bell, or sheaf-like aggregations of



FIG. 497. Various Forms of Uric Acid Crystals. (FREY.)



FIG. 498. Urinary Deposit, containing Uric Acid, Sodium Urate and Calcium Oxalate.

crystals, generally deeply pigmented so as to resemble cayenne pepper (Fig. 497).

(3) Calcium oxalate (Fig. 498). Colourless, transparent, highly refractive octahedral crystals (envelope-shaped). Insoluble in acetic acid, soluble in hydrochloric acid.

(4) Ammonium magnesium phosphates (in faintly acid or neutral urine). The crystals have been compared to knife-rests or coffin-lids (Fig. 499). They are soluble in acetic acid.

(5) Calcium hydrogen phosphate. CaHPO_4 . These are rare. They form prismatic crystals often arranged in rosettes. Easily soluble in dilute acetic acid. On adding a solution of ammonium carbonate, the crystals are eaten away and form an amorphous deposit.

(6) Tyrosine, fine needles in star-shaped bundles, and cystine, in regular hexagonal plates, may occur under very rare circumstances.

(b) *In Alkaline Urine.* (1) The commonest precipitate consists of earthy phosphates, amorphous, easily soluble in dilute acetic acid.

(2) Ammonium magnesium phosphate, or triple phosphate, is common in urine which has undergone ammoniacal fermentation.

(3) Acid ammonium urate (Fig. 499) may also occur in alkaline urine. On treatment with HCl it is dissolved and uric acid in crystals slowly separates out.

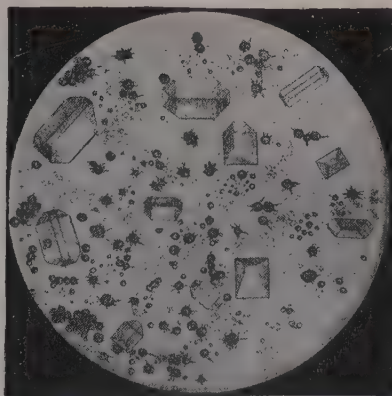


FIG. 499. Deposit of 'Triple' Phosphate and Ammonium Urate. (FUNKE.)

THE SECRETION OF URINE

With the exception of hippuric acid, and perhaps ammonia, all the constituents of the urine are formed in parts of the body other than the kidneys.

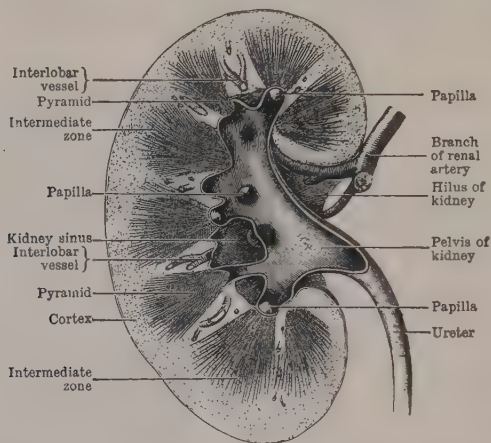


FIG. 500. Longitudinal Section of the Kidney, opening up the Kidney Sinus. The pelvis of the ureter and some of its calyces have been laid open as they lie within the sinus. (CUNNINGHAM.)

Extirpation of both kidneys leads to an accumulation of these specific urinary constituents in the blood and tissues. The work of the kidney is thus chiefly



FIG. 501. The Renal Artery and the Distribution of its Branches.

Anterior view of a left kidney. There are six main branches seen entering the kidney substance. Only one of these (the third) passes posterior to the pelvis at the hilum, also small arteries coming from the upper and lower calices. (After MAX BRODEL, *The Johns Hopkins Hospital Bulletin*, Jan., 1901.)

confined to an excretion of preformed constituents. Considered from a broad standpoint, the function of this organ is the preservation of the normal

composition of the circulating blood. Whenever the latter contains an abnormal constituent, or when any of its normal constituents are present in abnormal quantities, the kidney excretes the substance in question until the normal composition of the blood is restored. We have to determine the conditions which influence the quantity and quality of the urine secreted by the kidneys, and to ascribe to each element in these organs its proper share in the total work of the kidney.

Our views as to function are intimately dependent on our knowledge of the structure of the kidney. This organ is a branched tubular gland consisting, in man, of ten to fifteen nearly equal divisions, known as the Malpighian pyramids. In certain animals, such as the rabbit and rat, only one pyramid is present. It is divided into an outer portion, or cortex, an inner portion, the medulla, and between these the 'boundary layer,' containing the larger branches of the renal blood vessels (Fig. 500). From the outer boundary of the Malpighian pyramids of the medulla, a number of processes, the medullary rays, pass out into the cortex towards the surface of the kidney.

All parts of the kidney are made up of branched tubules embedded in scanty connective tissue and richly supplied with blood vessels (Fig. 501). Each tubule begins by a blind dilated extremity in the cortex, known as Bowman's capsule, which surrounds a bunch of capillary blood vessels, the glomerulus, the two together forming the Malpighian body. From Bowman's capsule a short neck leads into a proximal convoluted tubule, and this into a U-shaped portion which passes down in a medullary ray into the underlying portion of the medulla, and consists of straight descending and ascending limbs and the loop of Henle (Fig. 504). The ascending limb passes into a distal convoluted tubule, and this by a 'junctional tubule' joins with a number of others to form a straight 'collecting tubule.' Several of these unite to form the papillary ducts, which open on the surface of the papilla in the expanded part of the renal duct or ureter. The whole tubule consists of epithelium lying on a basement membrane; the epithelium varies in structure in different parts of the tubule. The bunch of glomerular capillaries is covered with a very thin layer of endothelial cells, and a similar layer forms the lining of Bowman's capsule. The convoluted tubules contain cells which are roughly cubical or cylindrical in cross-section, but do not present very definite cell outlines.

These cells, which are similar in the two sets of convoluted tubules, have long been distinguished as 'rodde epithelium' (Fig. 502) on account of the ease with which a radial disposition of rods or granules is demonstrated in their protoplasm. As ordinarily prepared, the free margin of these cells, where they abut on the lumen, is irregular. This appearance is due to the readiness with which the cells undergo alteration under the influence of different fixing reagents, especially of such as contain water. When properly fixed, it is seen that the rodde structure, as described by Heidenhain, is due to rows of granules arranged vertically to the basement membrane. Moreover, the free margin of the cells, instead of being irregular, consists of a well-marked striated border, formed of a number of very fine hairs closely set together and springing from a row of granules in the peripheral part of the cell (Fig. 503). The hairs, which make up the striated border (sometimes called the 'brush border'), have not been observed to present ciliary movement, and are probably comparable with the similar structures found clothing the free border of the epithelium of the intestinal villus. Such cells are characteristic features of the epithelium lining the urinary organs in all types of animals, and are well marked in the nephridia of worms. Besides these rows of granules, other granules are found, especially towards the free margin of the cell and round about the nucleus. Some of the granules appear to be of a fatty, others of a protein character. The descending limb of Henle's loop is narrow, and possesses flattened epithelial cells, while the ascending limb presents an epithelium similar to that of the convoluted tubules, but with less marked striation. The junctional and collecting tubules are lined with cubical or columnar cells with a clear protoplasm.

The marked differences between the structure of these various parts point to a differentiation of function. This conclusion is borne out by a study of the blood

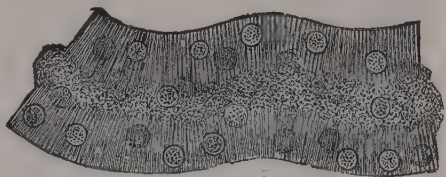


Fig. 502. A Portion of Convoluted Tubule with 'Rodde' Epithelium. (HEIDENHAIN.)

supply of the kidney. The large renal artery divides in the pelvis into four or five branches (Fig. 501), which pass up to the boundary zone and there give off arteries in different directions; those which run towards the surface are called the interlobular arteries. Each of these, which is an end-artery presenting no anastomoses with its fellows, gives off on all sides short wide branches, which pass to the glomeruli and constitute the *vasa afferentia* of these bodies. Each *vas afferens* has a thick muscular wall. The glomerulus itself consists of a number of wide capillaries invested by an extremely thin wall, which is sometimes said to consist simply of a protoplasmic film devoid of nuclei. The glomerular capillaries are collected together to form an efferent vessel, the *vas efferens*, which is narrower than the *vas afferens* but, like the latter, presents a well-marked muscular coat. The *vas efferens* breaks up again into a second set of capillaries, which ramify round the tubules of the cortex, bunches of long capillaries passing along the medullary rays and supplying the tubules of the medulla. From the capillaries of the tubules, the blood is collected again into veins, which leave the kidney partly by the cortex and capsular vessels, chiefly



FIG. 503. Cross sections of Convoluted Tubules from Kidney of Rat. (SAUER.)
A. During slight secretion. B. During maximal secretion.

by large venous trunks which join to form the renal vein at the hilum of the kidney. The kidney is richly supplied with nerves, which are chiefly distributed to the muscular walls of its blood vessels. Some authors have described a fine nerve-plexus surrounding the tubules and sending branches between and into the cells of the convoluted tubules themselves.

The main points in the above description of the structure of the kidney were made out by Bowman in 1840, and suggested the theories of urinary secretion both of Bowman and of Ludwig (1844), theories which have furnished the basis of all our subsequent investigation of the subject. Both observers appreciated the great difference between the membrane covering the glomerular loop and that of the lining membrane of the tubule, and both drew attention to the difference in the circulation in these two portions of the kidney. The glomerular capillaries, supplied with blood through a short wide artery, and drained by an efferent vessel smaller than the afferent, would represent a region of relatively high capillary blood pressure, whereas the pressure in the capillaries surrounding the tubules must be low and similar

to that in other capillary regions. Bowman therefore suggested that the urine arises from two sources, namely, one part containing the water and salts, produced by a process of filtration through the walls of the glomerular capillaries, and another part containing the specific urinary constituents,

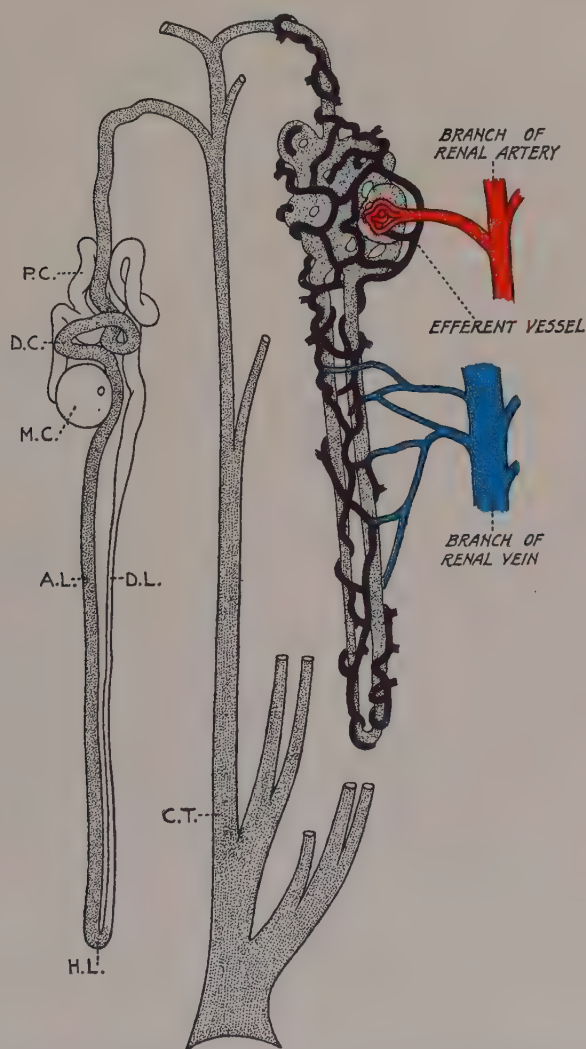


FIG. 504. Diagram of Two Uriniferous Tubules. On the left, the tubule is outlined from the capsule to the loop of Henle and is shaded from that point to the end of the collecting tubule. On the right, a diagram of the circulation is added. M.C., Malpighian capsule. P.C., Proximal convoluted tubule. D.L., Descending limb. H.L., Loop of Henle. A.L., Ascending limb. D.C., Distal convoluted tubule. C.T., Collecting tubule. (After CUSHNY.)

urea, uric acid, etc., secreted by the cells, probably of the convoluted tubules.

To Ludwig, on the other hand, it seemed possible, at first, to account for the whole process of formation of urine on the assumption that absorption, and not secretion, was the main function of the tubules. He imagined that the

whole of the urinary constituents passed in the glomerulus by a process of filtration from the blood to the urinary tubule. The glomerular transudate would represent, therefore, a very dilute urine, containing the crystalloids of the blood in the same concentration as in the blood and with no more urea than the blood itself contained. The great difference in urea content between the blood and the fully formed urine he ascribed to a process of concentration taking place in the fluid in its passage through the tubules, in which water and certain of the salts were reabsorbed; a process of reabsorption conditioned by the difference in protein content between the urine within the tubules and the lymph under low pressure on the outside of the tubules.

We know now that, in its original form, the theory of Ludwig is untenable. If a process of concentration occurred within the tubules, it would involve the performance of work by the cells lining these tubules, and could not take place as a result of mere differences of colloid content between the two fluids. If urine is dialysed against serum, there is, at first, a passage of water, not from urine to serum, but from serum to urine. The movement of water from one fluid to another through a colloid membrane depends on the relative osmotic pressures of the two fluids. It is easy to estimate this by determining the depression of freezing-point in the two fluids. Whereas serum ordinarily freezes at -0.56°C. to -0.59°C. , the freezing-point of urine is generally lower and may vary from this figure to as much as -4.5°C. For the production of urine from blood plasma, therefore, a certain amount of work has to be done, and the seat of this work we can locate only in the cells of the kidney. We may determine the *minimum* work necessary to form a certain amount of urine of a given concentration, by determining the energy that must be expended in order to concentrate the blood plasma to the same concentration and volume, and we can calculate it if we know the freezing-points of the two fluids. A depression of freezing-point $\Delta = -1^{\circ}\text{C.}$ corresponds to an osmotic pressure of 122.7 metres of water. To concentrate 100 c.c. of a saline fluid, such as urine, so as to halve its bulk and double its depression of freezing-point, *e.g.* from -1°C. to -2°C. , would therefore require the expenditure of work equivalent to that which would be required to compress 100 c.c. of a gas at a pressure of 122.7 metres of water to half its bulk. In this way can be determined the work necessary to change a fluid of $\Delta = -0.56^{\circ}$ (such as plasma) to one of -2.3° (urine). The work done in forming 200 c.c. of urine of this concentration from blood plasma would amount to 42.9 kgm. metres.

RELATIVE COMPOSITIONS OF BLOOD PLASMA AND NORMAL URINE IN MAN.

	Blood plasma, per cent.	Urine, per cent.	Change in concentration in kidney
Water	90-93	95	—
Proteins, fats and other colloids	7-9	—	—
Glucose	0.1	—	—
Urea	0.03	2	60
Uric Acid	0.002	0.05	25
Na	0.32	0.35	1
K	0.02	0.15	7
NH ₄	0.0001	0.04	400
Ca	0.008	0.015	2
Mg	0.0025	0.006	2
Cl	0.37	0.6	2
PO ₄	0.009	0.27	30
SO ₄	0.003	0.18	60

But the concentration in the kidney does not occur in this simple fashion. If we compare the composition of blood plasma with that of urine, we see that the constituents are concentrated to different extents.

If we added up the work required to produce the change in concentration of each constituent, we should arrive at a figure probably ten times as great as that given above.

The magnitude of this figure is, however, no argument against the reabsorption hypothesis, since the same amount of osmotic work would have to be done, whatever the way by which the urine is produced.

The large amount of work done, under some conditions, by the kidneys in the formation of urine, is indicated by measurements of the oxygen consumption of this organ. This usually amounts to 2 to 4 c.c. per gramme per hour, and in some forms of diuresis may be greater still (Fee and Hemingway).

The abandonment of Ludwig's view as to the mechanism of the concentration does not, however, place his theory out of court. The question that will still have to be discussed is whether the chief object of the tubules is the concentration of the fluid produced in the glomeruli, or whether they add to this fluid by a further secretory process, or whether they may not possibly possess both functions, and, in their various parts, alter the fluid flowing through them, either by addition or by withdrawal of water or dissolved constituents. The common point in the two theories is the sharp distinction which is drawn between the nature of the glomerular activity and the nature of the activity of the tubules. The questions which we have to decide by experiment are :

(1) The nature of the glomerular activity and the conditions which determine the amount of fluid formed by the glomeruli, and, especially, whether the energy required for the formation of the glomerular fluid is furnished by the heart, *i.e.* by the blood pressure within the capillaries, or by the endothelium covering these capillaries.

(2) The function of the tubules, whether they secrete or absorb, and what part is played in these processes by the various segments of the tubules, which differ so widely in their histological characters.

FUNCTIONS OF THE GLOMERULI

It is generally agreed that a watery exudation, free from protein, is formed in the glomeruli, and that this becomes concentrated on its way through the tubules, either by the absorption of water and certain salts, or by the secretion and addition of urea, uric acid, &c., as well as such salts as acid phosphates. As to the nature of the glomerular functions, two opinions have been held. According to the Ludwig school, the process is one of simple ultra-filtration, in which, under the pressure of the blood in the glomerular capillaries, the water and crystalloid constituents of the plasma are filtered through the glomerular epithelium, leaving behind the protein constituents. According to Heidenhain, the process involves the secretory activity of the glomerular epithelium. If we are to accept the opinion that the only function of the glomeruli is that of filtration, the energy for which is supplied by the blood pressure, certain conditions must be fulfilled.

(1) In the first place, the glomerular transudate must have a composition identical with that of the plasma *minus* protein—the concentration of the crystalloid constituents must be the same in the two fluids. There is a certain amount of evidence which tends to show that such is the case. Thus Wearn and Richards have succeeded in inserting a capillary pipette into the

Bowman's capsule of the frog's kidney, and so obtaining directly a small amount of fluid from the capsule. By micro-chemical methods they were able to show that in some cases, the concentration of chlorides in this fluid was approximately equal to that in the plasma, allowance being made for the protein constituents of the latter. In the majority of experiments, however, the chloride concentration in the glomerular fluid was higher than in the plasma: the cause for this is unexplained. The kidney of *Necturus*, which has very large capsules, has been similarly examined by White and Schmidt, and has given glomerular fluid which resembles that of the frog. The fluid in both these animals was also found to contain glucose, which is absent from the urine as it passes into the ureter.

In the frog's kidney, Bainbridge claimed to have excluded the action of the tubules by poisoning their epithelium. This was possible in consequence of the manner in which blood is supplied to the amphibian kidney, which receives its blood from two sources. A number of renal arteries

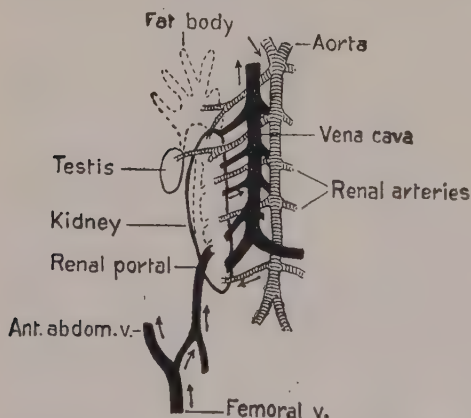


FIG. 505. The Vascular Supply to the Kidney in the Frog.

leaving the aorta enter the kidney and supply the whole of the glomeruli, the vasa efferentia from which pass, as in the mammalian kidney, into the intertubular capillaries. These, however, also have connections with the renal portal vein, shown in the Figure 505, and it is certainly possible, by perfusing the renal portal vein at a high pressure, to cause a flow in that direction. In Bainbridge's experiments, an artificial circulation of Ringer's fluid was maintained both through the renal arteries and through the renal portal vein. On adding a small trace of mercuric chloride to the fluid passing through the renal portal vein it was possible to poison the lining cells of the tubules. Under normal circumstances, the frog, unlike the mammal, secretes a hypotonic urine, *i.e.* one with a molecular concentration smaller than that of the blood plasma. After poisoning the tubules, the urine was found to be identical with the blood plasma (without its proteins), with the same concentration of chlorides, &c., as in the latter.

The description of the blood supply of the frog's kidney, on which these experiments were based, was that given by Nussbaum in 1878. Of recent years, there has been some difference of opinion as to the accuracy of that description. Woodland claimed that the tubules of the frog, like those of the mammal, were supplied by capillaries derived from the efferent arteriole of the glomerulus, and that the renal portal veins merely ran through the kidney as wide vessels which, together with the venules formed from the tubular capillaries, ultimately joined the renal vein. A rather similar view has been supported by C. S. Smith. Hayman, and Bensley and Steen, however, after the most careful enquiry, consider that Nussbaum's original description is substantially correct.

It has been possible to obtain somewhat similar evidence on the mammalian kidney. By connecting the artery of an excised kidney to the arterial side of a heart-lung preparation, a constant circulation of warm oxygenated blood can be maintained, the pressure, velocity and composition of the blood

supplied to the kidney being under control. The urine obtained in this way from the perfused kidney resembles normal urine in many respects, *i.e.* it contains urea, sodium sulphate, and certain colouring matters which appear in the urine in higher percentage than they are present in the circulating blood. The urine is, however, hypotonic and contains only 0.02 to 0.2 per cent. NaCl, as against the ordinary amount of 0.65 per cent. in the plasma of the circulating blood.

We have seen that, in the production of normal urine there must be an expenditure of energy on the part of the kidney, and this can be derived only from the processes of oxidation. If the fluid produced by the glomeruli is similar in its crystalline constituents and molecular concentration to the cir-

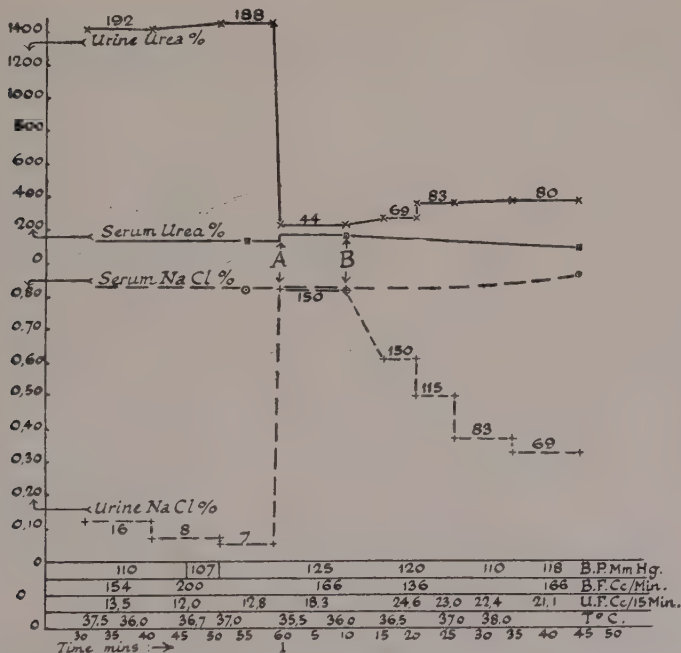


FIG. 506. Flow and Composition of Urine from a Perfused Kidney, and the effect of Cyanides thereon. Between A and B, the blood circulating through the kidney contained M/600 HCN. (STARLING and VERNEY.)

B.P. = blood pressure in renal artery. B.F. = blood flow through the kidney. U.F. = amount of urine in c.c. per fifteen minutes. T°C. = temperature of blood supplied to kidney.

culating plasma, it must undergo considerable alterations on its way down the tubules, involving the expenditure of energy on the part of the cells lining the tubules. It has already been pointed out that the effect of HCN is to reduce instantaneously the oxidative processes occurring in cells. If, in such a perfused kidney, the circulation be suddenly switched over to a pump, driving blood to which HCN in the proportion of M/600 has been added, it is found that the urine continues to be secreted and to flow from the ureter, generally in somewhat increased amount, but the urine so obtained resembles, in its composition, plasma *minus* protein, the percentage of chlorides, of urea, of sodium sulphate, being identical in the two fluids (*cf.* Fig. 506). We must assume that the effect of the HCN is to paralyse the cells of the tubules, so that we obtain from the ureter the glomerular transudate unaltered either by absorption or by secretion of any of its constituents.

(2) Even in the normal kidney with unpoisoned tubules, the constituents of the fully formed urine, as it appears in the ureters, after modification by addition or subtraction on the part of the tubular cells, must approximate more closely to the supposed glomerular transudate, the more rapidly the formation of this takes place: *i.e.* the quicker the flow of urine, the more nearly must its composition, reaction and osmotic pressure approximate to those of the blood plasma. The following experiment shows that this is the case. The osmotic pressure was measured by the depression of freezing point, Δ , of the two fluids.

A dog received 40 grammes of glucose dissolved in 40 c.c. of water. The Table represents the relative concentrations of urine and blood serum, at different stages in the diuresis thereby produced :

Time	Urine	Rate of flow, c.c. per 10 min.	Δ of urine	Δ of blood serum
11.30-12.0	10 c.c.	3.3	2.360	0.625 (at 12.0)
From 12.0 to 12.7 injected 40 grammes glucose into jugular vein				
12.7-12.15	35 c.c.	45	1.210	—
12.16-12.20	20 c.c.	50	0.975	0.700 (at 12.16)
12.20-12.30	52 c.c.	52	0.835	—
12.30-12.40	45 c.c.	45	0.825	0.700 (at 12.30)
12.40-12.50	22 c.c.	22	0.830	0.675 (at 12.40)
				0.675 (at 12.50)

(3) The total quantity of solids excreted in any given time must rise with any increase in the urinary flow—for whatever the activity of the tubules, the glomeruli must blindly turn out a certain proportion of salts with every cubic centimetre of fluid that they form.

The only factor which might prevent such a relation would be an active secretion of water or of hypotonic fluid by the tubules themselves. The fact that all experimenters have found this relation to hold, would tend to indicate that such a secretion of fluid by the tubules either does not take place or is insignificant in extent.

(4) We have seen that the protein constituents of blood plasma exert a certain osmotic pressure, amounting to about 4 mm. Hg for each 1 per cent. of protein content. Ordinary mammalian plasma would thus have a protein osmotic pressure of about 30 mm. Hg. This implies that, to filter off the fluid and crystalloid constituents of the plasma from the proteins, by means of a membrane impermeable only to colloids, would require a minimum difference of pressure of 30 mm. Hg between the two sides of the membrane. Thus, with a plasma containing 7 to 8 per cent. total proteins, the pressure of the urine in Bowman's capsule, and in the ureter, must be at least 30 mm. Hg lower than the pressure of the blood in the glomeruli. A direct determination of the latter figure has not yet been carried out. The anatomical arrangements are such as to bring this pressure up to a high value. Not only are the vasa afferentia very short, but the vasa efferentia are only two-thirds of the diameter of the vasa afferentia. Moreover, the sudden increase of bed, which ensues when the blood passes from the vas afferens to the bundle of capillaries, must itself diminish the fall of pressure in the latter, or might even cause an actual slight rise, owing to the transformation of the kinetic energy of the moving fluid into potential energy represented by pressure on the walls of the capillaries. It has been shown by White, however, that

this effect must be insignificant. In the frog, Hayman has estimated the pressures in the various vessels to be as follows :—

Aorta	37.3	cm. H ₂ O			
Afferent arteriole of glomerulus .	31.0	" "	or 84 per cent. of aortic pressure.		
Capillaries of glomerulus :	20.0	" "	54	" "	" "
Renal portal vein	5.2	" "	14	" "	" "
Renal vein	2.6	" "	7.1	" "	" "

L. Hill and McQueen, by direct experiment, arrived at 10 mm. Hg (= 14 cm. H₂O) as the glomerular capillary pressure in the frog. The colloidal osmotic pressure of the frog's plasma was estimated by White to be about 10 cm. H₂O, which would leave a margin of 4 to 10 cm. H₂O for filtration pressure. Krogh's estimation of the colloidal osmotic pressure of frog's plasma, with collodion of ordinary permeability, was of the order of 6 cm. H₂O, which would leave a still bigger margin. It seems possible that the pressure in the mammalian glomerular capillaries, with a free flow of blood from the vasa afferentia, may not be more than 10 mm. Hg below that in the main branches of the renal artery, while the pressure in the ureter is, under normal circumstances, presumably *nil*.

There may thus be, on the two sides of the glomerular membrane, a difference of pressure more than sufficient to cause a filtration of a protein-free fluid from the blood plasma coursing through these capillaries. On raising the pressure on the tubule side, the filtration ought to come to an end when the pressure approaches a figure which is 30 to 40 mm. Hg below that in the glomerular capillaries. A number of observers have found that urinary secretion ceases when the arterial blood pressure falls to between 40 and 50 mm. Hg. On the other hand, if the blood be diluted by the constant infusion of normal saline solution, so as to diminish its protein content, a secretion of urine may be obtained with a blood pressure as low as 18 mm. Hg. The urinary secretion can be stopped by raising the pressure in the tubules by means of ligature of the ureter. On applying the ligature, the secretion continues for a time, until the pressure in the ureter rises up to a certain point, when the secretion comes to an end. In one experiment, the following pressures were obtained in a dog which was secreting urine copiously under the action of diuretin. Manometers were connected both with the carotid artery and with the ureters, so that no outflow of urine was possible.

Arterial pressure	Ureter pressure	Difference
140 mm.	72 mm.	68 mm.
138 mm.	92 mm.	46 mm.
133 mm.	88 mm.	45 mm.

In this experiment, therefore, secretion came to an end with a difference of pressure between ureter and arteries of between 40 and 50 mm. Hg.

The absolute pressure attained within the ureter in any given experiment, after ligation of these tubes, will vary with several factors. In the first place, if the minimum filtration pressure is really conditioned by the colloid content of the blood plasma, it will be less the smaller the proportion of colloids in the plasma. In some experiments (Magnus) a flow of urine was observed with a blood pressure as low as 18 mm. Hg, but in this case the blood was extremely dilute, as the result of the continuous injection into the blood vessels of normal salt solution. Barcroft and Knowlton have shown that the diuresis brought about by injection of saline (Ringer's) solution is inhibited by mixing with the saline fluid colloids, such as gelatin and gum, which possess an osmotic pressure. Colloids such as starch, with no measurable osmotic pressure, have no such effect.

On the other hand, the ureters, or at any rate the urinary tubules, cannot be regarded as absolutely water-tight. Not only are the cells of these tubules capable of taking up fluid, but it is probable that, at high pressures, a certain amount of actual filtration takes place between these cells. This process of reabsorption will tend to diminish the actual pressure of the fluid in the ureters, so that the secretion of urine may apparently come to a standstill when there is still a difference of pressure, between blood and urine, considerably over 50 mm. Hg. Under such circumstances, the ureter pressure will be higher, and the difference of pressure between urine and blood less, the more rapid the formation of urine by the glomeruli. In a number of experiments by V. E. Henderson, it was found that the figure B.P. — U.P. tended, with increasing rapidity of urinary secretion, to approximate 40 mm. Hg. With a slow secretion, the flow of urine apparently ceased when there was as much as 80 mm. Hg difference of pressure on the two sides of the glomerular membrane.

We may conclude that, for the production of any urine by the kidney, a certain minimum difference of pressure is necessary between the blood in the glomeruli and the urine in the tubule, and that this difference becomes less the smaller the protein content of the blood. Since the only work required in the formation of a protein-free filtrate from the blood is that due to the osmotic pressure of the proteins themselves, and the observed difference of pressure during secretion is greater than this osmotic pressure, we are justified in concluding, provisionally at any rate, that the mechanical factors present at the upper end of the urinary tubule are sufficient to account for the production of a glomerular transudate free from protein, but containing the same proportion of water and salts as the blood plasma circulating through the capillaries.

(5) The amount of filtrate, so long as the ureter pressure is constant, must depend on the pressure and rate of flow of the blood in the glomerular capillaries. If the rate of flow is sufficient to effect an adequate renewal of the blood in the glomerular capillaries, the amount of filtrate, and therewith the amount of urine, must be proportional to the blood pressure in the capillaries. The pressure in the capillaries can be raised in either of two ways :

- (a) By increase of the driving force, *i.e.* the general blood pressure ;
- (b) By a diminution of the resistance to the flow of blood through the kidneys, as by dilatation of the vessels of this organ.

The blood flow through the kidney can be investigated, either by recording the total volume of this organ, or by determining the amount of blood which leaves it through the renal vein, according to the methods described in Chapter XXXIV.

It is necessary at the same time to take a record of the arterial blood pressure. It is evident that an expansion of the kidney may be caused by a rise of general arterial pressure or, the latter remaining constant, by a dilatation of the kidney vessels ; and, conversely, a fall of kidney volume may be due either to a fall of general blood pressure or to a constriction of the renal blood vessels. By taking these two records it is possible to tell whether a given increase of blood flow through the organ is of local or of general causation, *i.e.*, is active or passive. Thus, the volume of the kidney gives us an indirect clue to the pressure in, and the flow through, the kidney vessels as a whole, though admittedly it gives no information as to alterations in the distribution of the blood within the kidney. The flow through the vessels can be determined directly by a cannula in the inferior vena cava, all veins other than the renal being clamped, or, in the heart-lung-kidney preparation, direct from the renal vein.

The result of the experiments carried out on whole animals can be represented in the following tabular form :

Procedure	General blood pressure	Renal vessels	Kidney volume	Urinary flow
Division of spinal cord in neck	Falls to 40 mm.	Relaxed	Shrinks	Ceases
Stimulation of cord	Rises	Constricted	Shrinks	Diminished
Stimulation of cord after section of renal nerves	Rises	Passively dilated	Swells	Increased
Stimulation of renal nerves	Unaffected	Constricted	Shrinks	Diminished
Stimulation of splanchnic nerve	Rises	Constricted	Shrinks	Diminished
Division of one splanchnic nerve :				
(a) In dog	Unaffected	Dilated	Swells (?)	Increased
(b) In rabbit	Falls	Relaxed	Shrinks (?)	Diminished
Plethora	Rises	Dilated	Swells	Increased
Hæmorrhage	Falls	Constricted	Shrinks	Diminished

It will be seen that in every case where an increased kidney volume, attended with a rise of general blood pressure, is brought about, the urinary flow is at the same time increased.

The dependence of the urinary flow on the blood pressure is shown very clearly in some experiments by Richards. This observer placed a pump in the course of one renal artery of the rabbit, blood clotting having been prevented by the preliminary injection of hirudin. In this way, the circulation through the kidney was entirely under control, its pressure and velocity being known at any moment. He found that the amount of urine varied directly with the blood pressure and did not depend on the amount of blood flowing through the organ. Similar results were obtained by Starling and Verney in experiments on the heart-lung-kidney preparation.

It was objected by Heidenhain that if the process occurring in the glomeruli was one of filtration, ligation of the renal vein should increase the urinary flow, whereas this procedure is known to diminish, and soon stop the flow altogether. It must be remembered, however, that at any given time the glomerular capillaries contain but little blood, and with total cessation of the renewal of the blood, their contents must rapidly become so concentrated as to be little more than a mass of red blood corpuscles. No filtration of water and salts can take place unless there is a continual renewal of the fluid on the blood side of the filter.

All these considerations strongly support the view that the process occurring in the glomeruli is one of filtration, for which the energy is furnished by the blood pressure. It must be remembered, however, that the epithelial cells clothing the glomerular capillaries are alive and all their properties depend on the maintenance of this vitality. They will thus require oxygen for the maintenance of their physical qualities as a filtering membrane. This is shown by the experiments quoted above with HCN. During the first few minutes after the circulation of blood containing this substance has commenced, a fluid is obtained from the ureters perfectly free from protein, though resembling in all other respects the blood plasma circulating through the capillaries. In ten minutes' time the fluid is found to contain small traces of coagulable protein, which rapidly increases in amount as the circulation of the poisoned blood is continued. Complete obstruction of the renal artery not only stops the production of urine, but its effects last for some time after the obstruction has been removed, and the first portions of urine obtained when secretion is re-established are found to contain coagulable protein. In the same way, any damage to the glomeruli as a result of defective circulation, of imperfect oxygenation of the blood, or of inflamma-

tory and infective conditions of the kidney, is invariably associated with the passage of coagulable protein into the urine.

THE FUNCTIONS OF THE RENAL TUBULES

The production of the filtrate by the glomerulus is regulated entirely by its permeability, by the pressure and velocity of the blood through its capillaries and³ by the colloid content of the blood plasma. With any rise of general blood pressure the amount of this transudate is increased; with any fall it is diminished. The small qualitative changes, which are constantly occurring in the blood as the result of the taking of food or the activity of different organs, probably produce but little effect on the amount of glomerular fluid. But this transudate differs widely from the fully formed urine, as shown in the Table below and must therefore undergo considerable changes on its way through the tubules.

ABSORPTION IN THE TUBULES. According to Cushny, the whole of the changes by which the glomerular transudate is transformed into urine may be ascribed to processes of absorption occurring in the tubules, there being no need to assume the possession of secretory functions by this part of the kidney. He would, indeed, deny any fine discrimination to the kidney, and assume that the composition of the fluid absorbed is always the same, whatever the needs of the organism at the moment. In the Table below are given the changes which must be effected in the glomerular transudate in order to transform it into average urine, assuming that the only function of the tubules is one of reabsorption.

	67 litres plasma contain		62 litres filtrate contain in all	61 litres reabsorbed fluid contain		1 litre urine contains	
	Per cent.	Total		Per cent.	Total	Per cent.	Total
Water . . .	92	62 l.	62 l.	—	61 l.	95	950 c.c.
Colloids . .	8	5360 gr.	—	—	—	—	—
Glucose . .	0.1	67 gr.	67 gr.	0.11	67 gr.	—	—
Uric Acid . .	0.002	1.3 „	1.3 „	0.0013	0.8 „	0.05	0.5 „
Sodium . .	0.3	200 „	200 „	0.32	196 „	0.35	3.5 „
Potassium .	0.02	13.3 „	13.3 „	0.01	11.8 „	0.15	1.5 „
Chloride . .	0.37	248 „	248 „	0.40	242 „	0.6	6.0 „
Urea . . .	0.03	20 „	20 „	—	—	2.0	2.0 „
Sulphate . .	0.003	1.8 „	1.8 „	—	—	0.18	1.8 „

It will be seen that, while there is no absorption of urea and of sulphate, the whole of the glucose, a portion of the uric acid and the greater part of the sodium, potassium and chloride are absorbed. The absorbed fluid thus resembles Locke's fluid. According to this view, the constituents of the glomerular transudate, *i.e.* the diffusible constituents of the blood plasma, may be divided into two classes, 'threshold substances' and 'no-threshold substances,' the former being only excreted in the urine so far as their concentration in the blood exceeds a certain threshold value, while the others are excreted in proportion to their absolute amount in the plasma. Thus, of the threshold substances, the glucose of the plasma is normally below the threshold, and is therefore not present in normal urine. The sodium

chloride also comes within the threshold class, but its threshold is more frequently exceeded in normal conditions, and the excess is then eliminated. When the sugar of the plasma rises, as in diabetes, to 0.3 per cent., it appears in the urine and then undergoes concentration, just as urea does. Thus, so far as concerns the cells of the tubules, the no-threshold substances are not reabsorbed and must all escape by the ureter, whereas the threshold bodies are absorbed in different proportions, determined by their normal values in the plasma. The tubules absorb from the glomerular filtrate a slightly alkaline fluid containing sugar, amino-acids, chlorides, sodium and potassium in approximately the same proportions as they are present in normal plasma. "Thus the tubules, out of the glomerular filtrate, return to the blood the fluid best adapted for the tissues, and allow the rest to escape. If the plasma is

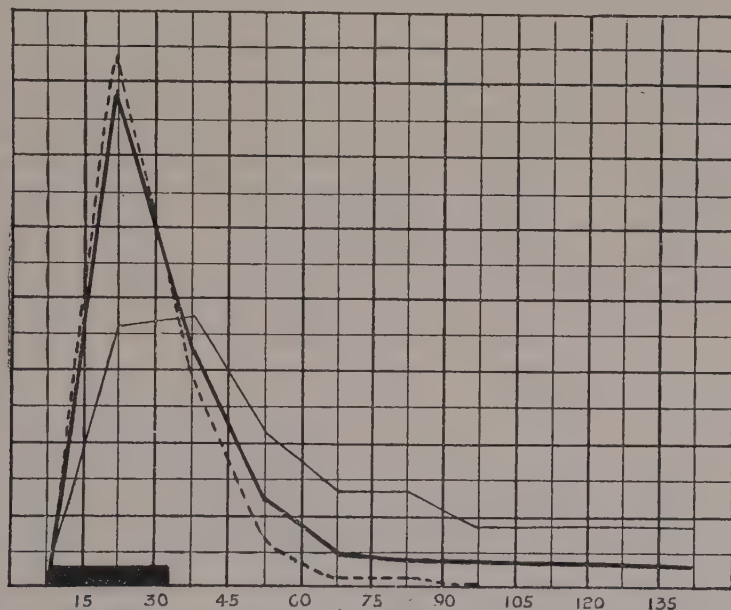


FIG. 507. Curves showing Excretion of Urine (thick line), of Sulphate Molecules (SO_4 , thin line), and of Cl Molecules (Cl , dotted line), after injection of 50 c.c. of a solution containing 1.775 grammes Cl and 4.8 grammes SO_4 per 100 c.c. The black line along the base marks the duration of the injection. (CUSHNY.)

too rich in sugar or chloride, the filtrate also contains those substances at or above the threshold value. The tubules, however, return them at the optimal or threshold concentrations, and the remainder passes into the ureters. If much water has been ingested and the filtrate is correspondingly dilute, the subtraction of the optimal solution leaves the excess water in the urine, along with the urea and other waste products" (Cushny).

There can be no question that reabsorption does take place in the tubules, affecting not only the water but also some of the dissolved constituents of the glomerular transudate. It was pointed out by Meyer that, if two salts such as sodium sulphate and sodium chloride were present at the same time in the glomerular transudate, any process of reabsorption should affect chiefly the more diffusible salt, namely, sodium chloride. Such a differential reabsorption would account for the much greater diuretic power of sodium sulphate as compared with sodium chloride. In certain experiments, Cushny pro-

duced a diuresis by the injection of equal parts of equivalent NaCl and Na_2SO_4 solutions into the veins of a rabbit. An increased flow of urine was produced, which lasted two hours and a half. The chlorides of the urine rose with the diuresis and reached their maximum at the height of the urinary flow. They then sank, and in some experiments had practically disappeared from the urine towards the end of the observation. The concentration of the sulphates, however, continued to rise in the urine to the end of the experiment. Thus, in the first of two identical experiments, when the rabbit was killed at the height of the diuresis, the serum contained 0.547 per cent. chlorine and 0.259 per cent. sulphate, while the urine contained 0.372 per cent. chlorine and 0.546 per cent. sulphate. In the second, in which the rabbit was killed when the rate of the urinary flow had considerably diminished, the serum contained 0.493 per cent. chlorine and 0.191 per cent. sulphate, while the urine contained 0.094 per cent. chlorine and 2.0 per cent. sulphate. These results are illustrated in Fig. 507.

The difference between the two salts can be made still more striking if the process of secretion be slowed by increasing the pressure within the tubules by partial obstruction of one ureter. Thus, in one experiment, where diuresis was produced by the injection of 30 c.c. of a solution containing 5.85 per cent. NaCl + 14.2 per cent. Na_2SO_4 , the right ureter was partially clamped so as to make the right kidney secrete against a pressure of 31 mm. Hg. The following results were obtained:

		Urine, c.c.	Cl, grm.	SO_4 , grm.
4.37 till 4.47	{ Left kidney	24	0.0809	0.1080
	{ Right kidney	8	0.0142	0.0667
	Difference (absorption)	16	0.0677	0.0413

The reabsorption of chlorides by the tubules is definitely proved by the experiment of Wearn and Richards on the frog's kidney, and of White and Schmidt on the kidney of *Necturus*. The plasma of the latter animal contains about 0.36 per cent. of NaCl, whereas the urine contains only about 0.026 per cent.; when dog's red blood corpuscles were injected into the Bowman's capsule, they were seen to be rapidly washed down into the tubules, by the flow of glomerular filtrate; when the corpuscles entered the tubule they were at once laked, presumably because so much chloride was abstracted from the fluid that it acted almost like water.

We must conclude that the tubular epithelium possesses the power of modifying the glomerular transudate, not only by the absorption of water, but also by the absorption of dissolved constituents, and that the relative permeability of the cells to the constituents is at any rate one factor in determining the substances absorbed. It is not however the only factor. The function of the kidney is to preserve the normal constitution of the body fluids, by turning out those substances which are abnormal or present in too great an amount. The behaviour of the tubule cells with regard to any given substance will therefore depend to a certain extent on the previous nutritive history of the body.

If, for instance, in consequence of the administration of sodium chloride in large quantities to the animal during the few days preceding the experiment, the body is overloaded with this salt, it becomes an abnormal constituent and the kidney secretes a urine far richer in sodium chloride than is the blood plasma. Moreover, when diuresis is produced in such an animal

by the injection of equivalent quantities of sodium chloride and sodium sulphate, there is no diminution of the NaCl in the urine towards the end of the diuresis, but its percentage rises steadily as the rate of urinary flow diminishes. On the other hand, a total deprivation of sodium chloride extending over several days, although not altering to any large extent the percentage amount of this salt in the blood plasma, leads to a total disappearance of the salt from the urine, the whole of the sodium chloride present in the glomerular transudate being reabsorbed on its way through the urinary tubules.

The power of absorption possessed by the cells of the tubules is not indefinitely large, and the urine can therefore never exceed a certain concentration, at which its osmotic pressure just equals the absorptive power of the cells. This limiting concentration differs in different animals, the cat being able to absorb against a resistance of fifty to sixty atmospheres, while the human kidney cannot concentrate against a resistance of more than twenty-five atmospheres. The presence of any inabsorbable substances in the glomerular filtrate, *e.g.* urea, sodium sulphate, or phosphate, must therefore limit the absorption owing to the osmotic resistance they offer to the absorptive powers of the cells. These substances will therefore act as diuretics. In the same way the threshold substances will act as diuretics, provided that they are present in the plasma in proportions above the threshold, so that they can no longer be absorbed by the cells of the tubules.

It has been objected to this view, by Heidenhain and others, that, if we exclude the occurrence of secretion by the cells of the tubules, we must assume that, of the seventy litres passing the glomeruli in the course of twenty-four hours, no less than sixty-eight litres must be reabsorbed in the tubules in the formation of two litres of urine. But Cushny points out that we have many analogies to this process in the body. Thus, the liver throws into the duodenum 500 c.c. of fluid in twenty-four hours, most of which is reabsorbed with the exception of the pigment. The urine of birds passes down the ureter as a clear fluid, but in the cloaca almost all the water is absorbed, leaving a thick paste of urine. Nor is the work out of proportion to the mechanism provided. In a cat fed on meat, 100 c.c. of urine contained as much solids as twelve litres of plasma filtrate, so that for twelve litres filtered through the glomeruli 11.9 were reabsorbed in the tubules. Since each kidney contains about 16,000 glomeruli,* the amount of fluid filtered by each glomerulus would amount to about 0.055 c.c. per hour. Of this, more than 0.0144 c.c. was absorbed in passing along 3 cm. of tubule, leaving from each capsule less than 1 mg. per hour to enter the collecting tubule (Cushny). This cannot be regarded as too severe a task, either for the glomeruli or for the tubules.

But it is impossible to explain the production of urine, and the variations in its constituents under different conditions, on this simple theory. Thus it is found that the degree of concentration of the 'no-threshold' substances, when we compare their content in the blood plasma and in the fully formed urine, is not identical, as it should be if the whole of them were filtered through the glomeruli and then concentrated simply by absorption of the water in which they are dissolved. Moreover, in the perfused kidney which is secreting a hypotonic urine containing a mere trace of NaCl, the chlorides in the circulating blood rise steadily in consequence of the loss of water

* This estimate of the number of glomeruli is probably too low. Direct counts of the glomeruli in the rabbit's kidney, by Hayman and Starr, show that each kidney contains upwards of 200,000 glomeruli. Each human kidney contains about 4,500,000 glomeruli [Traut].

through the kidney, so that the fluid reabsorbed from the glomerular transudate must have a greater concentration of chlorides than the latter, or than the blood plasma. The actual addition of sodium chloride to the circulating blood does not alter this relation. Moreover, if the theory were correct, the paralysis of the functions of the tubules should lead to an enormous increase in the amount of fluid poured out by the kidney. Even in the excised perfused kidney which is effecting only a four-fold or six-fold concentration of the urea of the blood, cutting out the action of the tubules should increase the amount of urine also four-fold or six-fold, since it reduces the percentage of urea in the urine to that present in the blood. But it is found that, on passing blood containing HCN through the kidney, although there is generally some increase in the urine obtained, this increase is never greater than 50 per cent., and in some experiments may be absent altogether. There seems, therefore, little doubt that, in addition to the processes of absorption, there are also processes of secretion taking place in the renal tubules. The evidence in favour of this conclusion may now be shortly passed in review.

SECRETION IN THE TUBULES. Histological examination of the kidney tubules shows a great diversity of structure in the epithelium with which they are lined. Small differences have been described between the cells of the first and second convoluted tubules, though these are nearly identical in structure. But in Henle's loop there are two different kinds of cells, and these again differ from those of the junctional and collecting tubules. If the function of the tubules were uniformly that of absorbing a Locke's solution from the glomerular transudate, one would expect a greater uniformity of structure in the lining epithelium. It may be regarded almost as an axiom that where we find differences of structure there are also differences in function.

In the cells of the convoluted tubules, various kinds of granules and of vacuoles may be distinguished. Gurwitsch divides these vacuoles into three classes:

- (1) Large granules staining densely with osmic acid, and probably rich in lecithin.
- (2) Smaller, very numerous granules, consisting of some form of protein material.
- (3) Large vacuoles lying close to the free margins of the cells, whose contents do not undergo coagulation with the ordinary fixing reagents, and therefore are free from protein, fat, or mucin. These vacuoles are especially marked in kidneys which are secreting at a great rate, in consequence of the injection of saline diuretics or of large quantities of normal salt solution. They have been regarded as excretory vacuoles, and as containing water or saline fluids which have been collected by the cells, and are being passed on by them to the lumen of the tubules.

In a secreting gland, such as the parotid, there is a marked change in the appearance of the granules, according as the gland is resting or actively secreting. No such changes have been discovered in the granules of the renal cells, and the vacuoles that have been described might be either in process of secretion or might be evidence of copious absorption of watery fluids from the lumen of the tubule.

As a rule it is impossible to trace any definite constituent of the urine on its way through the cells of the tubules. But if massive doses of uric acid, dissolved in piperazin, be injected intravenously into a rabbit, the kidneys, taken twenty to sixty minutes after the injection, present tubules full of uric acid concretions. In the medullary portion of the kidney, this uric acid precipitate is confined to the lumen of the tubules, but in the convoluted tubules granules of uric acid are to be found in the epithelial cells, especially towards their inner border. Under the same circumstances, masses of uric acid crystals are also found in the connective tissues between the tubules. It is therefore impossible to be certain that the granules observed within the epithelial cells are in process of excretion into, or of absorption from, the lumen. Modern methods have failed to substantiate the older observations as to the occurrence of uric granules under normal conditions in the cells of the convoluted tubules of the bird's kidney.

Heidenhain attempted to throw light on the excretory functions of the kidney by studying the mechanism by which it excretes certain dyestuffs, such as sodium sulphindigotate ('indigo carmine'). If the indigo be injected into the veins, it is excreted in a concentrated form, both by the liver and by the kidney, so that the urine assumes a dark blue colour. If the animal be killed when the excretion of the pigment is at its height and the kidneys be rapidly fixed with absolute alcohol (which precipitates the dyestuff), all parts of the kidney present a blue colour, which is especially marked in the medulla. Under these circumstances, the urine, which is being excreted by the glomeruli, rapidly carries down the dyestuff, wherever it may be turned out, into the tubules of the pyramids. In order to discover the exact locality of the cells involved in its excretion, we must stop the glomerular transudate by some means or other. This stoppage of the urinary flow can be effected in two ways, viz. by section of the spinal cord in the neck, so as to reduce the blood pressure to about 40 mm. Hg, *i.e.* below the minimum necessary for the production of urine, or by cauterising portions of the surface of the kidney by means of silver nitrate. If the indigo be injected into the veins after section of the cord, and the animal be killed half an hour later, and the kidneys fixed with absolute alcohol, they are found to be of a bright blue colour, although no urine has been secreted. On cutting into the kidneys, the colour is seen to be confined to the cortex, and, on making microscopic sections, granules of the pigment are found within the lumen and in the epithelial cells of the convoluted tubules. If the kidneys have been cauterised, the stain is confined to the convoluted tubules of the cortex only under those areas which have been cauterised, and where the glomerular functions have been abolished.

It can be, and is, objected to these experiments that they may equally well be brought about by absorption and not by secretion. If indigo carmine is turned out by the glomerulus, it will be in so dilute a solution that the glomerulus will not be stained. As the small amount of transudate descends the tubules it undergoes concentration, leading to precipitation of the dyestuff in the lumen of the tubules, and the granules in the cells may be the result, not of secretion but of absorption. Experiments of Starling and Verney on the perfused isolated kidney indicate, however, that Heidenhain's interpretation of the effects may, after all, be correct. In one experiment, with a copious flow of urine from the isolated kidney, it was found that secretion ceased entirely when the pressure in the renal artery was lowered to 37 mm. Hg. The pressure was then lowered another 5 mm. so as further to reduce the likelihood of there being any transudation in the glomeruli. Phenol red was then added to the circulating blood. This substance, like indigo carmine, is ordinarily turned out by the kidneys in a concentrated form. No urine was formed, but the dyestuff in the circulating blood diminished, and was found to have been deposited in a granular form in the cells of the convoluted tubules. Since, in this case, evidence of glomerular transudation was lacking, the dyestuff appears to have been taken up by the cells from the lymph, and ultimately from the blood bathing the outside of the tubules. When the tubules were paralysed by the addition of HCN to the blood circulating through the kidney, the urine obtained, which was isotonic with the blood plasma, contained about 60 per cent. of the concentration of the dyestuff present in the plasma. The same concentration is obtained if the plasma be filtered through a colloidal membrane, 40 per cent. of the dyestuff being adsorbed by the plasma proteins, and therefore not capable of passing with the water through the filtering membrane.

By taking advantage of the peculiarities of the renal circulation in amphibia, evidence of another kind can be obtained for the possession of secretory functions by the cells of the tubules. If all the renal arteries be divided or ligatured, the glomeruli, as was shown by Nussbaum, are entirely cut out of the circulation, though the tubules then receive some venous blood through the renal portal vein. Nussbaum stated that ligature of all the renal arteries caused cessation of the urinary secretion, which could be reinduced by injection of urea. He concluded that urea, with water, was secreted by the tubules, whereas peptone, sugar, and hæmoglobin were turned out by the glomeruli. Beddard showed that after *complete* obstruction of the arteries, no urinary flow could be induced, even with subcutaneous injection of urea. No doubt the blood supply to the tubules was inadequate to maintain their vitality, and there was, in fact, a rapid destruction of the tubular epithelium. But Bainbridge and Beddard made another series of experiments of the same description, in which the frogs, after ligature of the renal arteries, were kept in an atmosphere of pure oxygen. Under these circumstances sufficient oxygen was available *via* the renal portal vein, and no desquamation of the epithelium resulted; injection of urea now produced a small flow of urine, even when, by subsequent injection of the blood vessels, it was proved that every glomerulus had been cut out of the circulation.

Experiments by Bensley and Steen on the excretion of dyes by the frog's kidney, suggest that these are actually secreted by the cells of the proximal convoluted tubule, and that there is absorption of water, and perhaps of threshold substances, in the distal convoluted tubule. In these experiments, the kidneys were observed under the microscope at intervals after the injection of indigo carmine or phenol red. Some of the renal arteries were tied, so that parts of the kidney had no glomeruli functioning. In these, the dye was seen to appear in vacuoles in the cells of the proximal tube, and these then passed out into the tubule. When indigo carmine was given first, and phenol red after it, the first dye was displaced outwards into the tubule by the second, which followed it along the whole tube, both becoming concentrated as the distal tubule was traversed.

A consideration of all the experimental data relating to urinary secretion warrants the conclusion that, in the glomeruli, a process of filtration takes place, by which water and the soluble diffusible constituents of the blood plasma are separated from the proteins. The volume of transudate which is formed is probably not of the dimensions required by the hypotheses of Ludwig and Cushny, and may indeed be little more than that of the urine which passes into the bladder. The energy for this process of filtration is furnished by the heart beat, the amount of filtrate depending on the colloid content of the plasma and on the pressure of the blood in the glomerular capillaries. This latter factor can be altered within wide limits, being raised by dilatation of the vas afferens or contraction of the vas efferens, and *vice versa*.

It appears too that the arterioles, and perhaps the capillaries, are endowed with contractility, so that the condition of any one glomerulus may vary from time to time. If the frog's kidney be observed directly under the microscope, glomeruli come into view and then disappear again, according to the state of blood flow through their capillaries.

On its way down the tubules the glomerular filtrate undergoes extensive alteration in character, some of its constituents, water, salts and sugar, being absorbed, while other constituents such as urea, uric acid, creatinine, and

probably phosphates and ammonia, are added to it, so that we obtain finally a fluid which is adapted, as an excretion, to the general needs of the body.

THE ADAPTATION OF THE RENAL FUNCTIONS

When we examine the urinary secretion in the intact animal, we cannot but be struck with the manner in which its amount and concentration are adapted to the needs of the body as a whole. Under salt hunger, chlorides disappear from the urine: when large quantities of water are taken by the mouth, there is a rapid excretion of a very dilute urine, so that the constitution of the body, and of its fluids, is not altered by the water ingested. When there is increased production of acids in the body, as occurs on a large protein diet, or under abnormal conditions, such as diabetes, the excess of acid is excreted in the urine, which thus becomes highly acid. If, in spite of this, the bicarbonate of the plasma is lowered, less chloride is eliminated, so that the osmotic pressure of the plasma is unaltered. Alkaline salts taken by the mouth, or formed in the body as a result of the oxidation of the salts of the vegetable acids, cause the secretion of an alkaline urine. Normal urine contains no sugar, although this substance is an unfailing and necessary constituent of the blood plasma in a concentration of about 0.1 per cent. If, however, the sugar in the blood rises by a small amount, namely, to 0.2 per cent., the excess of sugar is at once excreted in a highly concentrated form by the kidneys, so that this substance may occur in the urine to the extent of 6 or 7 per cent.

The simplest explanation of the varying activity of the kidney would be to assume that this organ reacts to very minute changes in the composition of the circulating blood. A consideration of all the facts shows, however, that the matter is more complicated. When a large amount of water is taken by the mouth, it is often impossible to detect any change in the composition of the blood plasma, though the kidney is secreting large quantities of extremely dilute urine. It might be thought that there was a slight lowering in the molecular concentration of the plasma, to which the kidney was sensible, but which was not appreciable by our methods of analysis. It is possible to bring about a lowering of molecular concentration by injecting small or large quantities of a hypotonic salt solution directly into the blood. Under these circumstances, not only is there no increased secretion of urine, but the amount formed by the kidney generally diminishes. In the same way, when a large quantity of sodium chloride is taken, the result is a temporary rise in the salt concentration of the plasma which may last a day or two. This is then succeeded by an increased excretion of salt by the kidney, but this occurs at a period after the salt concentration of the plasma has returned to normal. The salt ingested seems at first to pass into the tissues, and is only got rid of from these by an increased excretion after a considerable latent period.

We have seen that the isolated perfused kidney secretes urine containing only traces of sodium chloride, although the content of this salt in the blood serum is rising steadily throughout the experiment. If, in such a perfusion, the blood is also circulated through a head, the volume of urine is speedily reduced, and its chloride content correspondingly increased (Fig. 508), but this does not occur if the pituitary body has first been removed from the head. A similar condition occurs in the disease known as *diabetes insipidus*, where the patient passes large quantities of watery dilute urine and suffers very intense thirst as a consequence. Diabetes insipidus is often associated with demonstrable alterations, of a destructive nature, in the pituitary

body, probably in its posterior lobe. Excision of the pituitary body may often, for a time, at any rate, bring about a similar condition, namely increased formation of urine and disappearance of chlorides from the urine; and it is interesting to note that injection of pituitrin into a patient with diabetes insipidus, or addition of a small amount of the extract of the posterior lobe of the pituitary body to the blood circulating through the excised kidney, cures the condition, the urine diminishing in amount while the chlorides in it rise considerably and in some cases even exceed the percentage amount of chlorides in the plasma. These and similar facts remind us that the kidney is not an isolated organ, guided in its activity merely by the nervous system, through its influence on the blood vessels, or by the composition of the blood, but that it is played upon by chemical messengers or hormones, which reach it from different parts of the body according to the

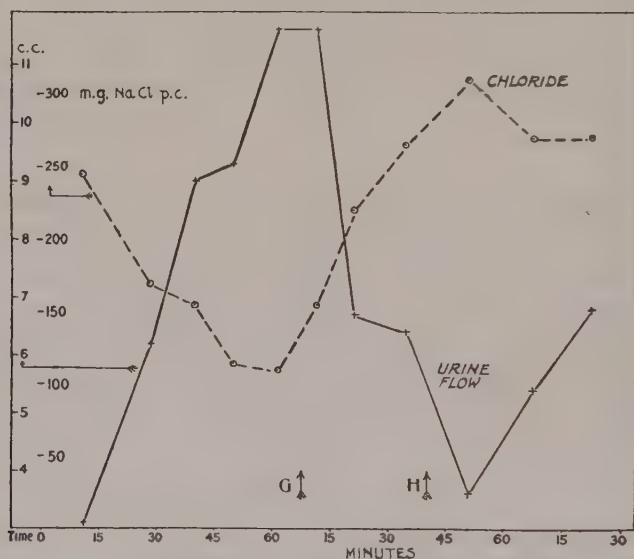


FIG. 508. Volume (in c.c. per 15 min.) and Chloride Content of Urine (as m.g. NaCl per cent.) of Dog's Kidney in Heart-Lung-Kidney Perfusion. At G a dog's head was switched into, and at H out of, the circuit. (VERNEY.)

chemical condition in which these parts happen to be. One of these hormones, regulating the urinary secretion and composition, would appear to be formed normally in the posterior lobe of the pituitary; but it is possible that other hormones, at present unknown, also act upon the kidney and determine the degree to which absorption and secretion of the different constituents of the urine are carried out by the several parts of the tubules.

ACTION OF DIURETICS

Attempts have been made to illuminate the problem of renal secretion by studying the action of diuretics, *i.e.* substances which, injected into the blood stream or absorbed from the alimentary canal, increase the secretion of urine. A large increase in the urinary flow can be brought about by the intravenous injection of saline diuretics such as sodium sulphate or potassium nitrate, or neutral crystalloids such as urea or sugar.

Two types of factor might be concerned in promoting an increased flow of urine. These are :

- (1) Increased glomerular transudation from mechanical causes, *e.g.* rise of pressure in the glomerular capillaries, increase of blood flow, reduction of protein content of the blood, or the opening-up of glomeruli previously closed by constriction.
- (2) Reduced absorption (or increased secretion ?) in the tubules, such as may, conceivably, happen when the pituitary hormone is reduced.

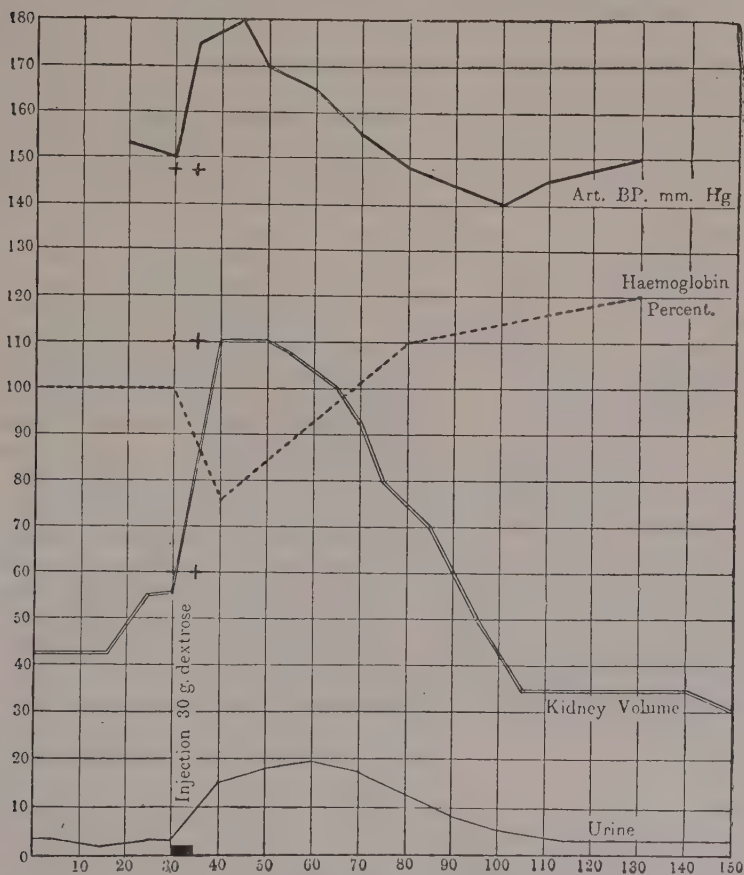


FIG. 509. A Comparison of the Effects of Intravenous Injection of 30 grammes Glucose in Concentrated Solution, on the Arterial Blood Pressure, the Concentration of the Blood, the Kidney Volume, and the Urinary Flow.
Abscissa = time in minutes.

When a concentrated solution of salt is injected into the circulation, the total volume of the circulating fluid is soon increased by the addition to it of water derived from the tissues, *i.e.* a condition of hydræmic plethora is set up, just as if a large bulk of normal saline fluid had been injected into the circulation. So long as this hydræmic plethora continues, so long is there a rise both in arterial and venous pressures and in the velocity of the circulating blood. The kidney placed in an oncometer shows a great increase in volume. While the plethora lasts, there are mechanical conditions at work in the kidneys, *i.e.* rise of pressure, greater rate of flow, and diminished concentration of plasma—

all of which would concur in producing an increased glomerular transudation. With certain salts, such as sodium chloride, the diuresis may be coterminous with the hydræmic plethora, but with other members of this class, such as glucose, the diuresis always outlasts the plethora, so that the continued augmentation in the secretion of urine leads to an actual concentration and diminution of the volume of the circulating blood, as is shown in Fig. 509. If the kidney be placed in an oncometer, it is found that the dilatation of the kidney outlasts the plethora, and comes to an end only with the cessation of the increased urinary flow. Since, however, increased secretion of urine involves dilatation of the tubules, and therefore swelling of the whole kidney, the rise of the oncometer during diuresis is no proof that there is still a greater circulation through the kidney. In fact, however much glomerular change may be concerned in the initial increase in the urinary flow, the terminal

increase must be ascribed to reduced absorption in the tubules. As we have already seen, every substance which is not absorbed from the glomerular filtrate by the tubules must act as a diuretic, since it will oppose osmotic resistance to the absorbing powers of the cells. Thus the no-threshold substances, urea, and sodium sulphate, nitrate, and phosphate, will, in any concentration, act as diuretics. The threshold substances will produce diuresis so long as their concentration in the plasma surpasses their normal threshold value.

With regard to the specific diuretics, such as caffeine, the question is not quite so clear. In most cases, injection of caffeine in the rabbit brings about a dilatation of the kidney and a proportional increase in the secretion of urine. But cases have been recorded in which expansion of the kidney occurred without any increase in urinary flow, and, on the other hand, augmented urinary flow without any increase in the kidney volume, or even in the rate of blood

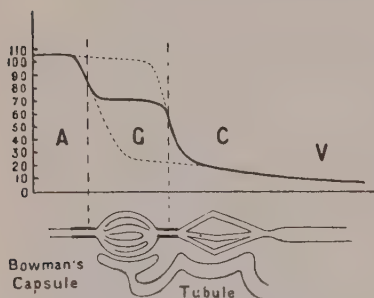


FIG. 510. Diagram (after MORAT) to illustrate the effect of Active Changes in the Vasa Afferentia and Efferentia on the Pressure in the Glomerular Capillaries.

If the vas afferens constricts, the pressure will be represented by the lower dotted line. On the other hand, constriction of the vas efferens would raise the pressure in the glomerulus till it almost equalled that in the renal artery, as is shown by the upper dotted line.

- A. Arteries.
- C. Tubular capillaries.
- G. Glomerular capillaries.
- V. Vein.

flow through the kidney. The general rule, however, is that a greater rate of blood flow is obtained *pari passu* with the increased urinary flow; and a consideration of certain peculiarities in the renal circulation must prevent us from laying too much stress on apparent exceptions to the rule. A dilatation of the afferent vessels, and a slight constriction of the efferent vessels, would cause a considerable rise of pressure in the glomerular capillaries, and a consequent increased transudation, without necessarily altering to any marked extent the total circulation of blood through the whole organ.

An important factor in regulating glomerular activity is the contractility of the afferent and efferent arterioles of the glomeruli. It was shown by Richards and Schmidt that under certain circumstances, glomeruli of the frog's kidney can actually be seen to constrict so that no blood passes through them. Intermittent closure of the glomeruli is to some extent spontaneous, but the number so closed is greatly increased by stimulation of the kidney nerves, by various reflexes, and by adrenaline.

Hayman and Starr have counted the number of glomeruli in the rabbit's kidney which were open to circulation when in the normal state, and also after administration of caffeine. They find that, whereas in the normal state, from 50 to 90 per cent. of the glomeruli are patent, all of them are opened after a dose of caffeine. After adrenaline, on the other hand, only 10 per cent. of them may be in use, and the urine flow was much reduced.

On the other hand, it seems probable that many diuretics—of which caffeine may be one—act by altering the activity of the tubules. If we accept the idea that the main function of these structures is that of secretion, we may assume that the diuretics increase their secretory power. It is more simple, however, to assume that any action these substances possess on the tubules is one of paralysis, complete or partial, of their powers of absorption. Thus the action of phlorhizin may be assumed to paralyse the absorptive powers of the tubular cells for glucose—*i.e.* to reduce glucose for this particular kidney to the state of a no-threshold substance. The glucose in the glomerular transudate, in passing through the tubules, may thus be concentrated sixty to a hundred times. Since glucose is made in the body, and supplied to the circulating blood in proportion to the needs of the body, so as to maintain its concentration in the plasma at a definite height, the loss of sugar in the urine will be continued, and the percentage in the plasma will not tend to diminish progressively with the increased secretion of urine, as would occur, for example, in the case of urea. We may assume that different diuretics have similar powers of paralysis on the absorptive mechanisms of the tubules, either general, or confined, as in the case of phlorhizin, to one or other of the normal constituents of the plasma. In the same way, pituitrin appears to depress the chloride-absorbing functions of the tubules while exalting their powers of water absorption.

There is even a possibility that some types of diuresis may be caused by temporary suspension of the secretion of the posterior lobe of the pituitary body. Such causes would act only indirectly on the kidney, and since a simple diuresis by water-drinking operates without there being any demonstrable dilution of the blood, an indirect action of such a nature might be suggested. It has been shown by Fee that this is unlikely, however, since he has succeeded in causing water diuresis in decerebrated dogs, whether the pituitary was present or not. In his experiments, moreover, removal of the pituitary body did not cause diuresis.

THE PHYSIOLOGY OF MICTURITION

The urine as it is formed passes through the ureters to the bladder, where it gradually accumulates, and is voided at intervals.

The ureters enter the bladder at or near its base, at the two posterior angles of the trigonum. Their entrance is oblique, so that a valvular orifice is formed, which effectively prevents reflux of urine from bladder to ureter. The ureters are lined by transitional epithelium. The muscular coat is composed of three layers of unstriated fibres, a middle circular coat lying between external and internal longitudinal coats. If the ureter be exposed in the living animal, contraction waves are seen to pass along its muscular coat from the pelvis of the ureter to the bladder, driving the contained fluid in front of them. The frequency of the contractions is increased by warming the ureter, and to a certain extent by distension, so that the waves are more frequent when the secretion of urine is profuse. Rhythmic waves of contraction are observed also in the excised ureters, when these are kept warm

in normal saline solution. These contractions are probably myogenic. The ureters are supplied with nerve fibres from the splanchnic nerves by way

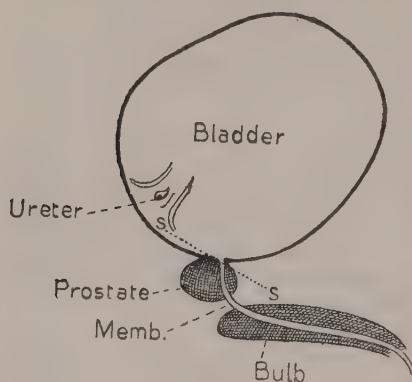


FIG. 511.

of the renal plexus, and at their lower ends from the hypogastric nerves. Stimulation of the latter as a rule increases the rhythm of the contraction presented by the lower end of the ureter. The splanchnic nerves have been stated to produce both acceleration and inhibition of the contractions at the upper end; their action is, however, uncertain. It is by the rhythmic advancing waves of contraction of the ureter that the urine is continuously passed on to the bladder, so that the pelvis of the ureter is kept empty of fluid whatever the position of the animal.

The bladder is lined by transitional epithelium, closely adherent to the underlying muscular coat. It is usual to describe in the latter three layers of muscular fibres :

(1) An outer layer, composed of bundles running longitudinally from the neck of the bladder to the fundus, sometimes distinguished by the name of the *detrusor urinae*. At the neck of the bladder these bundles send some fibres to be attached to the pubes as the pubo-vesical muscles. On the dorsal surface some bundles, in the male, pass on to the prostate and the urethra, while in the female they end in the tough connective tissue in the urethro-vaginal septum.

(2) The middle layer, which is the thickest of the three, is composed of fibres arranged circularly and forming a continuous layer.

(3) The inner layer is thin and incomplete, and is composed of anastomosing bundles of fibres, with meshes in between them, which are covered by the folds of the mucous membrane. The bundles of fibres run freely from one layer to the other, and there is no doubt that the name of *detrusor* ought physiologically to be applied to the whole of the three coats, which act as one in diminishing the capacity of the bladder.

At the base of the bladder, the structure of the wall is modified over the triangular region lying between the orifices of the ureters and of the urethra (the *trigonum*) by the differentiation here of fibres which serve as a sphincter and prevent the escape of urine. Over the trigonum, the mucous membrane of the bladder is smooth and closely adherent to the subjacent muscular fibres, which themselves are much more closely packed than in the rest of the bladder wall. From these muscular fibres, the most important sphincter, the *sphincter trigoni*, is formed. Bundles of muscle fibres pass from the trigonal muscle obliquely forwards and downwards (the individual being considered in the erect posture), and form a loop around the orifice of the bladder, lying on the ventral side of the bladder below and quite distinct from the thick coat of circular fibres belonging to the bladder itself (SS, Fig. 511).

This sphincter is the most important mechanism for the retention of urine. If a catheter be passed into the urethra no urine escapes until its orifice has actually entered the bladder. The wall of the urethra is surrounded by circular muscular fibres which, by their tonic contraction, will also tend to prevent the escape of urine along the canal. This urethral muscle is strengthened by two sphincter muscles, which are voluntary and composed of striated fibres. The chief one, the *compressor urethrae* (or *sphincter urogenitalis*), forms a flat ring around the second part of the urethra, extending in the male from the prostate to the bulb, where its function is taken up by the bulbo-cavernosus.

The bladder is therefore supplied with a powerful muscular wall, the contraction of which will cause its evacuation, and with sphincters of two kinds, one involuntary, the *sphincter trigoni*, at the upper neck of the bladder, and two voluntary, the *sphincter urogenitalis* and *bulbo-cavernosus* muscles, which can empty the lower parts of the urethra. In man, after destruction of the first part of the urethra by suprapubic prosta-tectomy, the compressor urethrae is the competent sphincter.

The nerve supply of the bladder (Fig. 513) is derived from two main sources, namely, from the hypogastrics (sympathetic) and from the pelvic visceral nerves or *nervi erigentes*. The upper four lumbar nerves send white rami communicantes to the lateral chain of the sympathetic, and thence to the collateral ganglia, which are grouped round the inferior mesenteric artery to form the inferior mesenteric ganglion. Most of the fibres

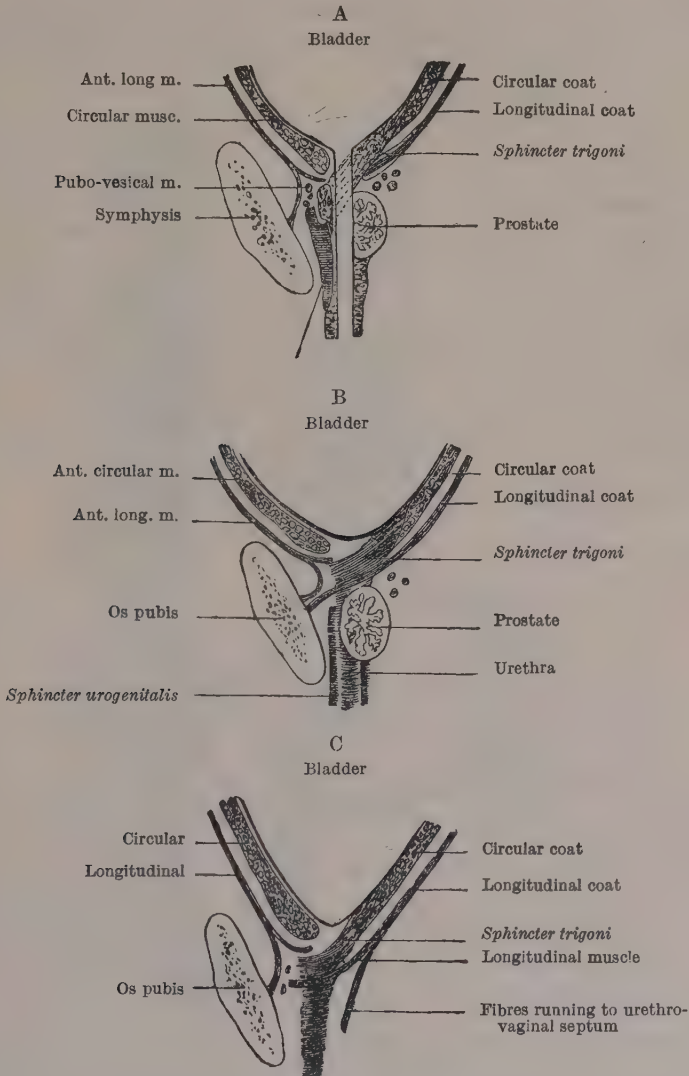


FIG. 512. Sagittal Sections through Neck of Bladder.
(METZNER after KALISCHER.)

A. In middle line (male). B. Slightly to left of middle line (male).
C. Ditto (female).

end in this collection of ganglion cells, and a new relay of axons passes, by the hypogastric nerves, into the pelvis on each side of the rectum and ends in a plexus, the hypogastric plexus, at the base of the bladder. From this plexus, fibres pass to the bladder wall. The pelvic visceral nerves are derived from the second and third sacral nerves. They pass directly to the hypogastric plexus and are carried with branches of this plexus to the neck of the bladder. The fibres do not run directly from the spinal cord to their ending in the bladder wall, but are interrupted by cells situated peripherally, partly in

the hypogastric plexus, but chiefly in the walls of the bladder itself. Both sets of fibres also supply the rectum and the colon, and carry efferent impulses to the bladder. Afferent impulses from the bladder travel in both, but chiefly in the pelvic visceral nerves.

The afferent and efferent nerves of the urethra travel in the pudic nerves and in the hypogastrics.

THE FILLING OF THE BLADDER. Under normal circumstances, the sphincters at the neck of the bladder are in a state of

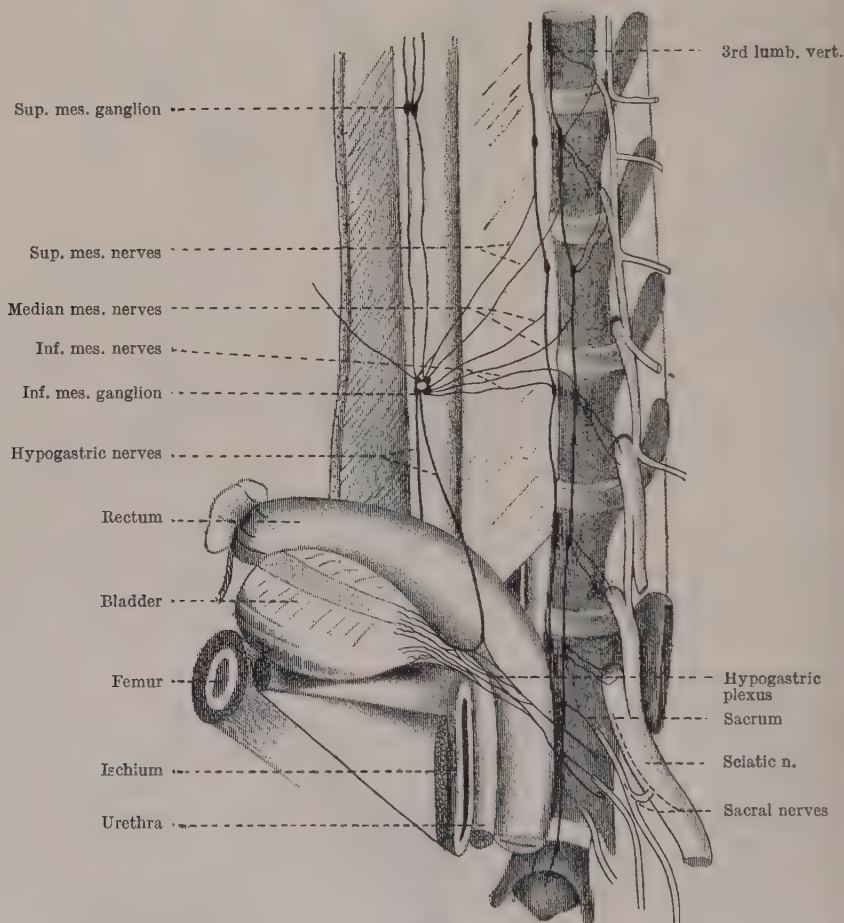


FIG. 513. Nerve Supply to Bladder of Cat. (Nawrocki and Skabitschewsky.)

tonic contraction, presenting a resistance to the emptying of this organ. Thus, it requires a considerably greater pressure in the bladder to overcome the resistance of the sphincters during life than after death of the animal. In some cases, after death they may permit the passage of urine when the pressure in the bladder is only about 20 mm. water, whereas, in the normal animal, the pressure has, as a rule, to be at least 160 mm. of water before any escape takes place. The urine, therefore, as it is secreted must accumulate in, and distend, the bladder. An extending force applied to an unstriated muscle fibre has a double effect. In the first place, if the stretching force is applied very slowly, a considerable increase in length of the muscle may occur with

the application of a very small amount of force. If, however, the force be applied more rapidly, the sudden increase of tension acts as a direct excitant to the muscle, causing it to enter into contraction, which may be tonic or rhythmic. The effect of the entry of urine into the empty bladder on the tension in this organ will depend, therefore, on the rapidity with which the kidneys are secreting. Under normal circumstances, micturition occurs in man when the intravesical pressure has risen to about 150 mm. water. Under these conditions, the bladder will contain between 230 and 250 c.c. of urine. If, however, the secretion of urine has occurred very rapidly, or if the bladder be unusually excitable, the same pressure may be attained with a much smaller bladder content, and if the bladder be artificially distended by the injection of fluid through a catheter, 50 c.c. of fluid may suffice to raise the pressure to this level. As the urine is slowly secreted, the bladder wall at first gives to the incoming fluid, so that a considerable amount can be stored without any marked rise of pressure. Later on, the pressure begins to rise more rapidly, and finally attains a pressure of between 120 and 150 mm. water. At this point, the second effect of the stretching of the muscular wall makes its appearance. A manometer connected with the bladder shows a series of rhythmic contractions of the muscular wall (Fig. 514), each lasting

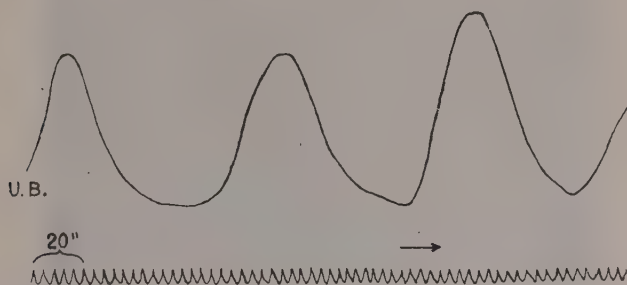


FIG. 514. Tracings of Rhythmic Contractions of Urinary Bladder.
(SHERRINGTON.)

about a minute, at first slight in extent, but becoming more marked as the distension of the bladder augments. In a bladder entirely cut off from its connection with the central nervous system, these automatic rhythmic contractions gradually increase in force, until one of them suffices to overcome the resistance presented by the tonically contracted sphincter. A partial emptying of the bladder therefore takes place, but before the bladder has been emptied, the pressure falls below that necessary to overcome the resistance of the sphincter, so that there is always, under these circumstances, a certain amount of residual urine left in the bladder. This is the condition found in animals when the lower part of the spinal cord has been extirpated, or in man when the same part of the central nervous system has been destroyed as the result of accident or disease.

THE MECHANISM OF EVACUATION OF THE BLADDER.

In the denervated bladder, the factor finally causing partial evacuation is the gradual increase in the intravesical tension, from the accumulation of fluid in this viscus. The same factor is prepotent in determining the onset of normal micturition in an animal with the nervous connections of its bladder intact. Apart from the control of the higher centres, micturition will take place each time that the tension in the bladder has reached a certain height, viz., about 15 cm. water, the amount of fluid in the bladder at the time depending, on the one hand on the rate at which the fluid has

entered this organ from the ureters, on the other hand on the irritability of the bladder wall itself and of the nervous centres concerned with its motor innervation. The effect of the gradual accumulation of fluid and rise of tension is twofold. In the first place, it acts on the bladder wall, causing rhythmic contractions of ever-increasing intensity; in the second place, the mere stretching of the bladder originates impulses in the sensory nerve-endings in its wall, and these are reinforced at every rise of tension caused by the rhythmic contractions. These impulses travel up to the nervous centres, and are summated until they result in a sudden discharge of efferent impulses of two kinds, namely:

- (1) Motor impulses to the whole musculature of the fundus of the bladder.
- (2) Inhibition of the tonic contraction of the sphincter and urethral muscles. The resultant of these two processes, the contraction of the detrusor and the relaxation of the sphincter, is a complete emptying of the bladder, and the act is completed by the contraction of the involuntary and voluntary

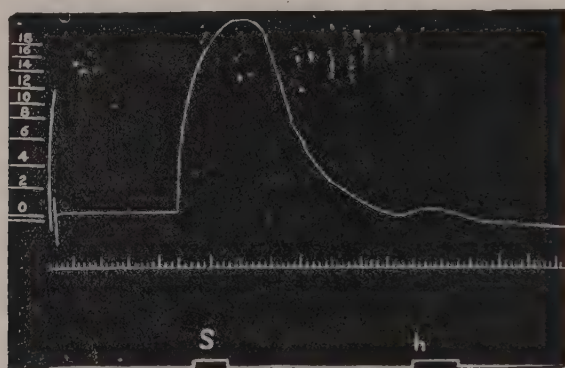


FIG. 515. Curve showing Rise of Pressure in the Bladder caused by Stimulation of *s*, Sacral Nerves; *h*, Hypogastric Nerves. (FAGGE.)

The scale indicates centimetres of water.

muscles surrounding the urethra and causing complete expulsion of the contents of this tube.

ACTION OF THE PELVIC VISCERAL NERVES. Excitation of the peripheral end of one pelvic visceral nerve causes a strong contraction of the same side of the bladder, sometimes extending also to a slight extent to the contralateral half. When both pelvic nerves are stimulated simultaneously, contraction of both sides of the bladder causes a rise of pressure in its interior (Fig. 515) which is sufficient to overcome the resistance of the sphincter and to cause a complete emptying of the bladder. There is no doubt, therefore, that these nerves are the most important for the act of micturition.

Observations on man would support the view that an active relaxation of the *sphincter trigoni* is a necessary part of the act of micturition. Thus, in experiments by Reyfisch, a rigid catheter was introduced into the bladder, which was fully distended with fluid. On withdrawing the catheter until its opening lay just outside the bladder in the posterior urethra, the flow of urine stopped. The man, however, was able to micturate directly he was told, and to stop again at will. It was impossible in this case for any of the urethral muscles to be concerned, since the rigid catheter impeded their action. The relaxation of the sphincter must therefore be brought

about by impulses descending the pelvic visceral nerves, which we may regard as motor to the detrusor, and inhibitory to the sphincter, of the bladder.

Section of the nerve on one side causes no abnormality in micturition. After three weeks, stimulation of the intact nerve causes contraction of the whole bladder, owing to the outgrowth of preganglionic fibres from the sound trunk to the decentralised ganglia of the opposite side (Elliott). Section of both nerves paralyses micturition, but power of partial evacuation of the bladder may return in a few weeks. If the hypogastrics be now cut, or even the sacral cord extirpated, the bladder is not completely paralysed, but its evacuation becomes unconscious and incomplete.

ACTION OF THE HYPOGASTRIC NERVES. These nerves show marked differences in their action, according to the animal which is the subject of investigation. In the dog, the hypogastric nerves cause a strong contraction of the muscle fibres at the base of the bladder, especially of the trigonum and of the *sphincter trigoni*. When these nerves are stimulated simultaneously with the pelvic visceral nerves, a great rise of intravesical tension may be induced without any flow of urine taking place. On the other hand, in the rabbit and the cat these nerves cause an inhibition of the bladder wall. In other animals they may excite either contraction or relaxation (or both) of the detrusor. They always contain motor fibres to the sphincter of the bladder as well as to the constrictor fibres surrounding the urethra. Where this effect is tonic, micturition must be associated with a central inhibition of their tonic activity. On the other hand, the retention of urine and the distension of the bladder may be aided by a reflex dilatation of the bladder wall and a reflex constriction of the sphincter, excited in each case through these nerves.

Normally therefore, both sets of nerves are called into action. The hypogastrics play an especially active part during the accumulation of urine in the bladder, while the pelvic visceral nerves are necessary for the complete evacuation of the bladder which occurs at micturition.

THE REFLEXES OF MICTURITION. The investigations of Barrington have revealed five reflexes concerned in micturition, viz. :—

(1) *Contraction of the bladder* when its internal pressure approaches 10 cm. of water. The afferent and efferent paths are in the pelvic nerves.

(2) *Contraction of the bladder*, even when only partially full, as a result of running fluid through the urethra. This ensures that when micturition is started by the first reflex, it will normally be continued to completion. The afferent path is the pudic, the efferent the pelvic nerve.

(3) *Contraction of the bladder* (slight), when the first part of the urethra is distended. Both paths are in the hypogastrics.

(4) *Relaxation of the urethra* when fluid passes along it. Both afferent and efferent paths are in the pudic nerves.

(5) *Relaxation of the urethra* when the bladder is distended. The afferent path is in the pelvic nerves, the efferent in the pudic.

It will be seen that each of these reflexes, except the third, is capable of giving rise to the remainder, and so collaborating to ensure normal micturition.

In the adult, the processes of retention and evacuation of urine are modified and controlled by voluntary effort. The normal action of the sphincter mechanism may be aided by the contraction of the perineal muscles, which keep the urethra closed. The reflex process of evacuation may be set in motion by voluntary contraction of the abdominal muscles, by which the pressure in the bladder is increased and the normal sphincter action overcome.

THE CENTRAL CONTROL OF THE BLADDER. A nerve centre, which presides over the tonus and contraction of the bladder, is situated in the lumbo-sacral spinal cord. If this centre and its connections be intact, micturition may be carried out even after section of the cord in the dorsal region, but according to Barrington, the process of micturition is always imperfect in animals or man after section of the cord in any part of its course. In fact, the normal reflex powers depend on the integrity of the paths connecting the lumbosacral cord with the hind-brain and lower part of the mid-brain. When these are divided, or the higher centres injured, the emptying of the bladder remains incomplete. The spinal centre can be excited reflexly by stimulation of any sensory nerve, such as the sciatic or the fifth nerve. In many cases where, in consequence of obstruction to the passage of impulses from the higher parts of the central nervous system, micturition is delayed, this act may be excited by the application of cold or hot sponges to the perineum, and it is well known that irritation of the pelvic organs in children may give rise to reflex involuntary micturition.

Barrington finds in cats that normal micturition is lost after destruction of a small area of the midbrain situated a short distance ventral to the internal edge of the superior cerebellar peduncle, and extending from the level of the posterior end of the aqueduct in front to the level of the motor nucleus of the fifth nerve behind.

CHAPTER XLI

THE SKIN AND THE SKIN GLANDS

In all classes of animals, the skin performs two functions. In the first place, it serves to protect the more delicate underlying parts from injury and from penetration or invasion by foreign organisms. In the second place, it serves as a sense organ, and is richly supplied with nerves, by means of which the activities of the body as a whole may be brought into relation

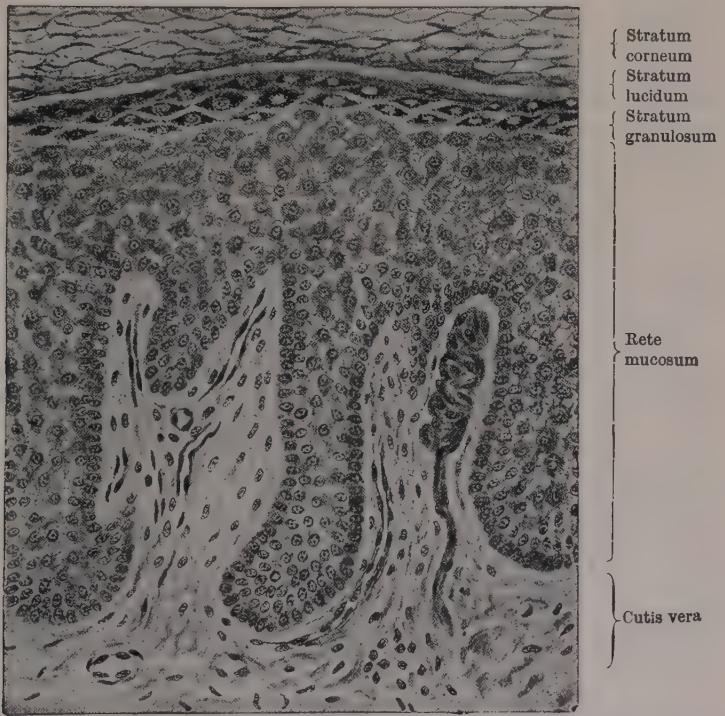


FIG. 516. Vertical Section through the Skin of the Palmar side of the Finger, showing two Papillæ (one of which contains a Tactile Corpuscle) and the deeper Layers of the Epidermis. Magnified about 200 diameters. (SCHAFER.)

with the changes going on in the environment and affecting the external surface of the body. In warm-blooded animals, the skin plays an important part in the regulation of the body temperature, since the loss of heat from the body must occur almost entirely through its surface. In the present chapter we have to deal only with the first and third of these functions.

The development of the skin as an organ of protection shows wide modification in various classes of animals. Thus it may become the seat of formation of horny plates, as in the alligator; of poisonous glands, as in the toad; or of mucous glands, as in many

varieties of fishes. In warm-blooded animals, the development of hair from the deeper layers of the epidermis serves to diminish the loss of heat. Since the hair follicles are richly supplied with nerve fibres, the hairs act also as organs of sensation. In man, where the hairs are rudimentary, except in certain localities, practically only this tactile function is retained. The external layer of the skin in man consists of a tough horny layer formed by the keratinisation of the external layers of cells of the epidermis. The skin is composed of two parts, the epidermis and the cutis (Fig. 516). The epidermis is a stratified squamous epithelium. The deeper layers form the *rete mucosum*, being soft and protoplasmic, while the superficial layers forming the cuticle are hard and horny. The most superficial layer of the *rete mucosum* is formed of flattened cells filled with granules of a material staining deeply with hæmatoxylin and eosin, known as *eleidin*. This layer is called the *stratum granulosum*. Immediately superficial to this layer is another in which the cells are indistinct. The cells are clear in section and form what is known as the *stratum lucidum*. These two layers evidently constitute the intermediate stages in the transformation of the cells of the *rete mucosum* into the horny scales which make up the *stratum corneum*. The cutis, or corium, is composed of dense connective tissue, which becomes more open in texture in its deeper part, where it merges into the subcutaneous connective tissue. The most superficial layer of the corium is prolonged into minute papillæ, over which the epidermis is moulded. These papillæ contain, for the most part, capillary blood vessels; a few contain touch corpuscles, special organs of tactile sensation. The blood vessels of the skin form a close capillary network immediately at the surface of the cutis, sending up loops into the papillæ. All parts of the skin, except the palms of the hands and the soles of the feet, are beset with hair follicles. The hair follicles are small pits which extend downwards into the deeper part of the corium, being downgrowths of the *rete mucosum*. The hair grows from a small papilla of cells at the bottom of the follicle, the part of the hair lying within the follicle being known as the hair root. The hair itself consists of long tapering, horny cells, the nuclei of which are still visible, though the cell substance has been almost entirely converted into keratin.

In order to keep the cuticle supple and to preserve it from the drying effects of the atmosphere, it is kept constantly impregnated with a fatty material known as *sebum*. This material is formed by the sebaceous glands, which are distributed all over the surface of the skin wherever hair follicles are to be found, the mouths of the glands opening into the hair follicles. A sebaceous gland is a pear-shaped body, consisting of a secreting part and a short neck opening into the follicle. The gland proper is composed of a solid mass of cells. The outermost cells are flattened and generally show signs of proliferation. The cells lying internal to these are much larger, and their protoplasm is transformed into a network, in the meshes of which are granules which show the reactions of fat. Further inwards, the protoplasmic network diminishes in amount, while the fatty granules increase in size, so that, in the lumen adjoining the duct, we find only a mass of cell debris and masses of fatty material. It has often been thought that the secretion of sebum depended simply on a fatty degeneration of the cells. The granules, however, when they first appear, stain with acid fuchsin, but not with osmic acid, and one must regard the formation of sebum as an act of true secretion, in which the secretory granules are gradually transformed into the special constituents of the sebum. For it must be noted that the sebum is not a true fat, nor does it correspond in composition with the fat found in other parts of the body. It is true that it contains fatty acids, but these are for the most part in combination, not with glycerol but with higher alcohols, including ischolesterol. A somewhat similar material, known as wool-fat or lanoline, may be extracted from wool, as well as from the feather-glands of water birds, such as the goose and duck. It consists mainly of esters of ischolesterol. It presents many advantages over ordinary fat as a protective salve for the surface of the body. In the first place, it can take up a large amount, as much as 100 per cent., of water. In the second place, it is not attacked by micro-organisms, so that it does

not tend to become rancid or to furnish a nidus for the growth of these organisms on the surface of the body.

The secretion of sebum is a continuous process, though it is probably quickened in conditions of increased vascularity of the skin. The extrusion of the products of secretion is determined by the presence of unstriated muscle fibres, the *arrector pili*, which pass from the surface of the cutis obliquely over the outer surface of the sebaceous gland. When these muscle fibres contract, the hair is erected and a certain amount of the sebum squeezed out on to the root of the hair and the surrounding skin. This contraction will occur on faradic stimulation, or whenever cold is suddenly applied to the skin. The contracted condition of all the muscles of the hair follicles is shown by the 'goose-skin' produced under such circumstances. There is no evidence that the secretion of sebum is in any way under the control of the central nervous system.

THE SWEAT GLANDS. Under normal circumstances, in temperate climates the greater part of the water taken in with the food in the course of the day is excreted by the kidneys, a smaller proportion leaving by the lungs and by the surface of the skin. On an average we may say that about 700 c.c. are got rid of through the skin. The excretion of water by the skin is, however, mainly determined by the need for regulating the temperature of the body, so that the amount leaving in this way depends on the heat production of the body or on the external temperature, and is very little affected by alterations in the quantity of fluid drunk. A certain amount of water is constantly evaporated from the surface of the body as the so-called 'insensible perspiration.' If a man's body be enclosed in a vessel through which a current of air is passed, and the temperature of the air gradually raised, it will be noted that the amount of water given off rises slowly up to a certain degree and then mounts rapidly. The sudden kink in the curve is due to the commencement of the activity of the sweat glands, and we are therefore justified in regarding the insensible perspiration as being determined by evaporation of water from the surface of the cuticle itself, apart altogether from the sweat glands.

The sweat glands are distributed over the whole surface of the skin, and are especially abundant on the palm of the hand and on the sole of the foot. They are composed of single, unbranched, coiled tubes, which lie in the subcutaneous tissue and send their ducts up through the cutis, to open on the surface by corkscrew-like channels which pierce the epidermis. The secreting part of the tube consists of a basement membrane lined by a double layer of cells; the innermost of these are cubical and represent the secreting cells proper. Between the secreting cells and the basement membrane is a layer of unstriated muscle fibres. The duct of the gland has an epithelium, consisting of two or three layers of cells with a well-marked internal cuticular lining, but there is no muscular layer.

The sweat formed by these glands is the most dilute of all animal fluids. As collected, it generally contains epithelial scales and some admixture of sebum. After filtration, it forms a clear colourless fluid of a specific gravity of about 1003. It contains over 99 per cent. of water. Among the solid constituents, sodium chloride is the most prominent—it may contain from 0.3 to 0.5 per cent. of this salt. It is generally hypotonic as compared with the blood plasma. It may also contain small traces of protein. This constituent is especially marked in the horse. It generally contains also a small quantity of urea, which may become a prominent constituent in cases of renal disease. The quantity of sweat excreted in the day is very variable.

The secretion is under the control of the central nervous system and is almost entirely adapted to the regulation of the body temperature. The

nervous mechanism can be set into activity either centrally or reflexly. The most usual factor is a rise of the body temperature. If a man sits in a warm room, *e.g.* of a Turkish bath, the secretion of sweat commences as soon as the temperature of the body has attained a height of 0.5° to 1° C. above normal. During muscular exercise, the temperature will generally be found to be raised if it be taken at the instant that sweating has commenced. The effect of rise of temperature may, however, be either local or central, so that one arm enclosed in a hot-air bath may sweat while the rest of the body is dry. Under ordinary circumstances, the central stimulation by the warm blood is the predominant factor. This is shown by an experiment of Luchsinger. In the cat, sweating is to be observed only on the hairless pads of the front and hind paws. If one sciatic nerve be cut, and the animal be placed in a warm chamber, sweating will commence, as the temperature of the animal rises, in the three intact paws, while the paw with the nerve cut will be quite dry. Sweating, moreover, as has been shown by Kahn, may be induced in the cat's paws by warming the blood passing through the carotid arteries on its way to the brain, at a time when the temperature of the blood circulating through the rest of the body, including the paws themselves, has undergone no alteration. Sweating may also be aroused by asphyxia, and this result is found even in the spinal cat, *i.e.* after separation of the spinal centres from the medulla. The secretion of sweat resulting from stimulation of the sweat nerves, although generally associated with increased vascularity of the skin, is not entirely dependent thereon. Thus, even in the amputated limb, stimulation of the sciatic nerve may cause the appearance of drops of sweat on the pad of the foot. If the sciatic nerve be stimulated in the intact animal, the secretion of sweat which is produced is associated with constriction of the vessels of the skin, due to simultaneous stimulation of the vaso-constrictor nerves running in the sciatic nerve.

As Langley has shown, the sweat nerves run entirely in the sympathetic system. Leaving the cord by the white rami communicantes from the second dorsal to the third or fourth lumbar nerves, they pass into the sympathetic chain. Here the first relay of fibres ends in connection with the cells of the sympathetic ganglia, and a fresh relay of fibres, which are non-medullated, pass from the cells along the grey rami into the various spinal nerves, to be distributed to the whole surface of the skin. Adrenaline, however, is without action on the sweat glands. The secretion of sweat may be excited by the injection of pilocarpine, even after division and degeneration of the sweat nerves, so that this drug must act peripherally on the glands. Complete section and degeneration of all the nerves to a limb, however, greatly reduces the response to pilocarpine, because it also reduces the vasodilator response (Burn). The action of pilocarpine, as well as the effects of artificial stimulation of the sweat nerves, is abolished by the administration of atropine.

GASEOUS EXCHANGES THROUGH THE SKIN. In any animal with a thin moist skin, such as the frog, the absorption of oxygen and the excretion of CO_2 through the skin may be sufficient for the proper aeration of its blood, so that it may continue to live after the extirpation of its lungs. In man there is also a continuous output of CO_2 through the skin, but the amount leaving the body in this way is negligible compared with that which is exhaled through the lungs. The loss of CO_2 by the skin rises with increase of external temperature. Thus at a temperature of 29° to 33° C. the CO_2 output by the skin is about 0.35 gramme per hour, *i.e.* about 8.4 grammes in the twenty-four hours. When the external temperature rises above 33° C., the CO_2 output increases, so that at 34° it is doubled and at 38.5° it may

amount to as much as 1.2 grammes per hour (Schierbeck). It is just at this temperature of 33° C. that a secretion of sweat begins to be noticeable, so that it seems probable that the increased CO₂ output may be due to the secretion of sweat, which, like other body fluids, contains carbon dioxide that readily escapes from it on exposure to the air.

ABSORPTION BY THE SKIN. In order to test the alleged influence of baths containing medicinal substances in solution, many experiments have been made to determine whether absorption is possible by the skin. It may be regarded as established that the uninjured skin is impermeable to watery solutions of salts or other substances. On the other hand, it is possible to produce a certain amount of absorption by the application of substances dissolved in fatty vehicles. Thus, the administration of mercury is often carried out by the inunction of mercurial ointments, and the fact that mercurial salivation may be produced in these conditions shows that a certain amount of the mercury must have been absorbed. It is difficult to imagine that any appreciable amount of cod liver oil will be available for the nutrition of the infant when this substance is administered by rubbing it on the skin. On the other hand, the moist mucous surfaces, such as the conjunctiva or the mucous membrane of the respiratory passages, as well as raw surfaces of the skin, *e.g.* which have been deprived of their epidermal layer by the application of blisters, permit the rapid passage of substances in watery or oily solution.

CHAPTER XLII

THE TEMPERATURE OF THE BODY AND ITS REGULATION

IN dealing with the chemical changes in the body as a whole we have seen that the sum of the metabolic processes is associated with the evolution

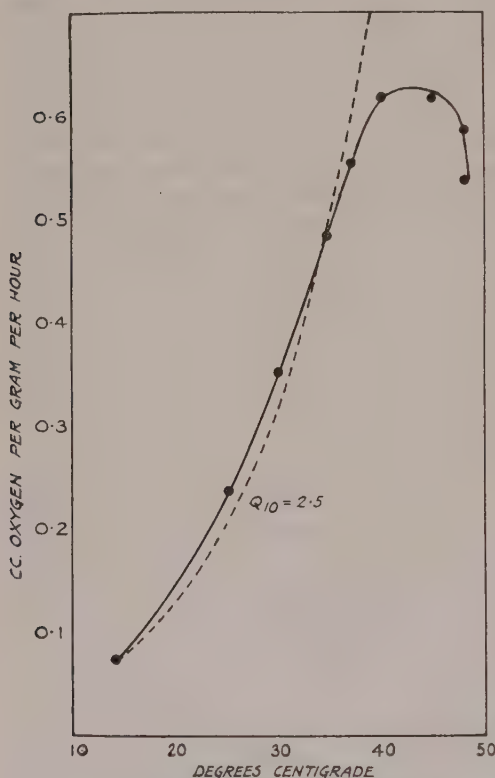


FIG. 517. Effect of Alteration of Temperature on Oxygen Usage of Plain Muscle (Guinea Pig Uterus). Abcissæ = temperature. Ordinates = c.c. oxygen per gram per hour. The dotted line represents the theoretical curve if the oxygen intake were increased two and half times for a rise of 10° C.

chemical changes which proceed in the living cells. Since all chemical processes are quickened by rise of temperature, we should expect to find that the heat produced in the metabolic processes of organisms would tend in itself to quicken these processes. In most chemical reactions a rise of about 10° C. would increase the velocity of reaction from two to three times, and the same rule is found to hold approximately over short ranges of temperatures for isolated living tissues. The diagram (Fig. 517) shows the influence of

of heat. In man, under normal circumstances, while doing moderate work, the total daily energy requirements amount to about 3000 Calories. The whole of this is derived from the oxidation of the food, the combination of its carbon and hydrogen with oxygen to form CO_2 and water, with the evolution of the corresponding amount of energy. Of this energy, only a small proportion, on the average about one-twentieth, leaves the body as mechanical energy, the rest being evolved in the form of heat and being expended in the maintenance of the body temperature, or in the warming of the surrounding medium.

The evolution of heat is not confined to the higher animals, but is common to all living beings. It is very evident, for instance, in the germination of peas or barley. The interior of a bee-hive is often 10° above that of the surrounding atmosphere. Whenever we can excite increased activity in an organ, we are able to show that such activity is associated with increased evolution of heat. This heat is derived from the

temperature on the chemical changes in plain muscle, as measured by the oxygen usage in c.c. per gram of tissue per hour. The increase in oxygen intake by the tissue is increased about two and half times for a rise of 10°C . until about 40°C ., beyond which temperature it declines rapidly owing to damage to the tissue. At about 48° the tissue becomes inexcitable (heat paralysis), but will recover again if cooled.

In the animal organism, we shall expect to find that the rate of the metabolism is also proportional to the temperature of the animal. This is universally the case, whether we are dealing with warm-blooded or cold-blooded animals. In cold-blooded animals, the temperature of the body,

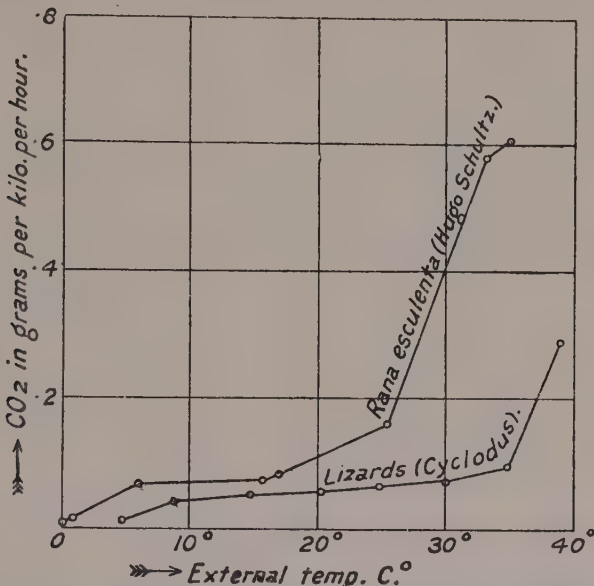


FIG. 518. Effect of Alterations in the Temperature of the Surrounding Medium on Output of CO_2 in Cold-blooded (Poikilothermic) Animals. (C. J. MARTIN.)

and therefore the rate of its metabolism and the amount of its heat production, is proportional to the external temperature (Fig. 518). The Table below gives the average CO_2 output per hour of five lizards placed in a chamber which could be maintained at varying temperature.

Temperature of bath	Temperature of lizards (average)	Mg. CO_2 produced in one hour per Kg.
5.0°C .	5.5°C .	13
9.0°C .	9.2°C .	42
15.0°C .	15.2°C .	53
20.5°C .	20.4°C .	55
25.0°C .	24.5°C .	64
30.0°C .	29.3°C .	78
35.0°C .	34.8°C .	97
39.0°C .	38.5°C .	292

It might be thought that such a reaction to change of temperature would result in a vicious circle. Since the animal is continually producing heat, and thus raising its temperature above that of its surroundings, one might expect to find that the higher the external temperature the more would the

temperature of the animal exceed it, until finally the latter would rise to such a height that the animal would die of heat-stroke, its tissues being damaged by the temperature ultimately attained. A certain protection is afforded to most cold-blooded terrestrial animals by the fact that their surface is moist, and that, with a rise of external temperature, the rate of evaporation from the surface increases, so that the quickened rate of cooling by evaporation more than corresponds to the rate of increase in the heat production, which would tend to raise the body temperature. Most of these animals, however, escape from any extreme rise of external temperature by burrowing underground or taking to the water, while, in plants, a rise of external temperature assists transpiration to such an extent that the temperature of the plant is generally several degrees below that of the surrounding atmosphere. The extreme variability in the metabolism of such animals implies a state of dependence of all the activities of the body on the environment, which would prevent the utilisation to the full of the available sources of energy. An animal whose metabolism was more or less independent of the surrounding temperature must have a great advantage over an animal liable to have his activities reduced and paralysed by a sudden spell of cold weather; this greater independence of the environment, which is characteristic of elevation of type, has been achieved by the warm-blooded animals, including man. Such animals are often spoken of as *homoiothermic*, i.e. animals possessing a uniform temperature, in contradistinction to the cold-blooded animals, which are *poikilothermic* and possess a temperature varying with that of their surroundings.

Amongst the warm-blooded animals, the body temperature may be very different according to the species. In birds, it is generally from 39° to 40° C.; in mammals it varies from 35° to 40° C. The temperature of man varies within slight limits about 37° C. (98·6° F.).

THE DIURNAL VARIATIONS IN THE BODY TEMPERATURE

In any animal the seat of heat production, e.g. a contracting muscle, must be warmer than an inactive tissue, and this again than a tissue from which heat is being rapidly abstracted, such as the skin. Owing, however, to the rapidity of the circulation of the blood, the temperature of the internal organs can be regarded as almost identical. The temperature of man is usually taken in the mouth, rectum, or axilla. In the mouth, the temperature is liable to fluctuation with the rate of breathing, the mouth being cooled by the passage of the air through the nasal cavities. There is also probably loss of heat through the cheeks. In order to determine the temperature in this situation, the mouth should first be kept shut for a few minutes, then the bulb of the thermometer inserted under the tongue and the lips kept closed on the stem of the thermometer for one to five minutes. Except in cases where the cutaneous vessels are much dilated, the temperature of a thermometer in the axilla takes a considerable time to rise to that of a thermometer in the mouth; it should never be left less than ten minutes in this situation. The following Table represents the temperature of different parts of the body:

SURFACE						
Skin covered with clothes	.	.	.	.	.	33° to 35° C.
Naked skin in bath at 5° C.	.	.	.	.	.	17° C.
" " " 25° C.	.	.	.	.	.	26·5° C.
MUSCLES 12 MM. BELOW THE SURFACE						
In bath at 5° C.	.	.	.	.	.	36·3° C.
" " 25° C.	.	.	.	.	.	36·9° C.

The body temperature of man shows variations of several tenths of a degree, according to the time of day at which the temperature is taken. The highest temperature is obtained about six or seven in the evening, and the lowest at about four or five o'clock in the morning. With these diurnal changes in temperature are associated parallel oscillations in the rate of metabolism, as shown by the utilisation of oxygen and the elimination of carbon dioxide. They are probably determined by the changes in the movement and tension of the muscles occurring during the waking hours. If the habits of a man or animal be reversed, so that he sleeps in the daytime and performs his normal vocation by night, it is possible to reverse also the direction of the diurnal variations in temperature. The temperature may also be affected temporarily by various acts, such as the taking of food or muscular work; the influence of the latter factor is often considerable. In many individuals a hard game of tennis suffices to raise the temperature to 39°C . (102°F .), and even the healthiest individual will show some change in his temperature as the result of exercise. Pembrey found that the act of marching led to a considerable rise in temperature, a rise which is apparently responsible for the discomfort and fatigue observed under such circumstances. Such a change in the body temperature is merely temporary in its effects, and is insignificant in comparison with the wonderful uniformity of temperature observed in men of all races and of all climes, under most varying conditions of food and activity.

Just as there are limits to the power of the organism to regulate its temperature when there is an excessive formation of heat within the body, so there are limits to the capacity to regulate the temperature when severe alterations occur in the temperature of the external medium. Thus if the body is subjected to excessive external cold, or if the loss of heat be increased by absence of clothes, by depriving an animal of its fur, or by immersion in a cold bath, the temperature of the body may sink continuously. In the higher animals this fall of temperature is very soon followed by paralysis of the highest nerve centres and by loss of consciousness. The centres in the medulla are later on affected, so that the respiration is slowed and the blood pressure falls. If the temperature does not fall too low, it is possible to revive the animal or man by checking the loss of heat, and by supplying artificial warmth. Recovery has, in fact, been observed in men in whom, as a result of exposure, the body temperature had fallen to 24°C . In the same way, exposure to extreme heat, especially associated with muscular exercise and increased production of heat in the body, may cause a rise of the body temperature. A man or animal, whose temperature is raised above the normal, is said to be in a state of pyrexia. A rise of 2° or 3°C . is associated with all the phenomena which characterise fever, *i.e.* quickening of pulse and respiration, malaise, headache, and loss of muscular power. If the temperature rise to a greater degree than this, the patient may lose consciousness, and death ensues at a temperature of about 44°C .

The very small variation presented by the body temperature of mammals, even under the influence of considerable variations in external temperature, or in the production of heat in the body, connotes an accurate adaptation between the production of heat in the body and the loss of heat from the body. The regulation of the temperature can be effected either by regulation of heat production, by alteration in the rate of loss of heat, or by a combination of both mechanisms. It will be convenient to deal under separate headings with these two methods of regulation.

THE REGULATION OF HEAT PRODUCTION

The reactions mainly responsible for heat production in the body are those associated with oxidation; the processes of disintegration, such as are effected by means of hydrolytic enzymes, account for only a very small part of the heat evolved.

In these processes of oxidation all the organs participate, the most important, especially in relation to the regulation of heat production, being the skeletal muscles. These represent more than half the total weight of the soft tissues of the body, and even during rest they are the seat of oxidative processes and therefore of heat formation. Heat formation varies with the state of tone of the muscles and is largely increased with every active contraction. The effect of muscular activity on the total output of energy of the body is well represented in the Table given on p. 516.

It is probable that, in relation to their size at any rate, the glands are still more effective as heat producers. The liver, and the blood flowing from the liver, have been stated to present a higher temperature than any other part of the body. On the other hand, the nervous system, although dependent on a constant supply of oxygen for its activities, does not appear to be the seat of extensive metabolic changes, nor does the heat produced in this system play any appreciable part in maintaining the temperature of the body.

The skeletal muscles are controlled by the central nervous system; if separated from their centres in the cord they become flaccid and rapidly atrophy. The heat production in the muscles is, therefore, also dependent on their connection with the central nervous system. If this connection be severed, either by curare or by section of the cord, or if the reflex play of impulses on the muscles be abolished by anæsthetics, the animal will react like a cold-blooded animal. The total metabolism of the body and the total production of heat then sink to a minimum, and are diminished by application of cold, or increased by application of warmth, to the surface of the body. On the other hand, in the intact animal, changes of temperature in the environment reflexly provoke changes in the opposite direction. Thus, exposure to cold increases, and to heat diminishes, the metabolism and heat production of the body. Though these changes, when extreme, affect the state of tone of the muscles, moderate exposures to cold lead to similar increases of metabolism by other means. Probably a discharge of adrenaline from the suprarenals is one of the chemical factors which brings about an increase in general metabolism under these circumstances.

The effects of variations in the external temperature on the metabolism of warm-blooded animals are well shown in the experiments from which the Tables given below are taken, on the CO_2 output in the *ornithorhynchus* (Martin) and the oxygen usage of a rabbit and of a curarised dog.

1. ORNITHORHYNCHUS. WEIGHT, 693 GRAMMES; SURFACE, 876 SQ. CM.

Temperature of environment	Temperature of animal	Difference in temperature, animal and environment	CO_2 per hour, in grammes	CO_2 per hour per 1000 sq. centims., in grammes
5	31.8	26.8	1.090	1.244
10	32.0	22.0	0.722	0.825
20	32.6	12.6	0.405	0.463
32	33.6	1.6	0.336	0.383
35	35.3	0.3	0.377	0.430

Rabbit (Pflüger).		Curarised Dog (Krogh).	
Rectal temperature °C.	c.c. Oxygen per Kg. and hour	Rectal temperature °C.	c.c. Oxygen Kg. and hour
22	457	14.1	134
26	608	22.7	300
37.5	888	28	495
37.6	839	32.2	620
38	763	37.2	812
38.8	738	39.9	700

In the first animal, where the regulation of the temperature of the body is effected almost entirely by changes in heat production, the effect

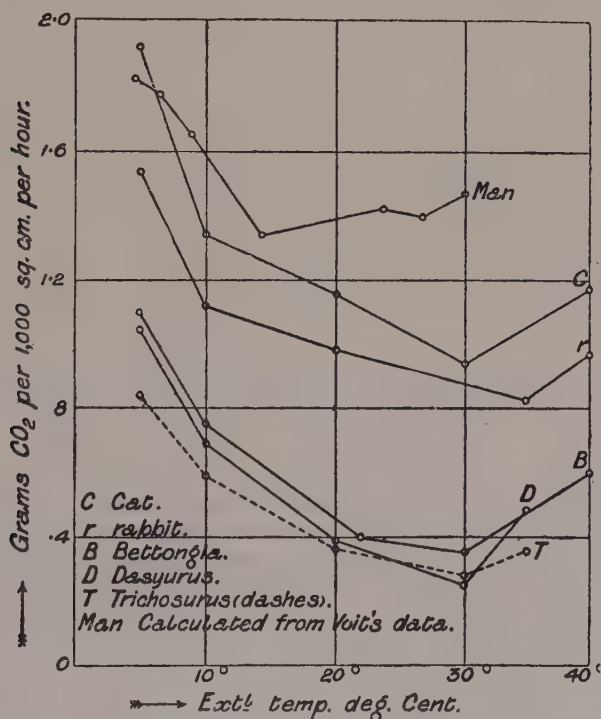


FIG. 519. Effect of Variations in the External Temperature on the CO₂ Output (per 1000 cm.² Body Surface) of Warm-blooded Animals. (C. J. MARTIN.)

of warming the environment of the animal on the CO₂ output is extremely marked. It will be noticed that the CO₂ per hour sinks continuously with rising temperature, up to 32° C. When the temperature of the chamber was raised to 35°, the temperature of the animal rose considerably, *i.e.* the regulatory mechanism was failing, so that the same effect was produced on metabolism as is observed in working with cold-blooded animals. This latter change, though less marked, is observed on exposing the rabbit to a gradually rising temperature. Here, however, the process of regulation is aided by alterations in the heat loss as well as in the heat production (Fig. 519). If the animals be observed whilst subjected to changes of tempera-

ture, it will be evident to anyone that the regulation is associated with changes in muscular activity. At 30° to 35° C. the animals will lie perfectly flaccid, breathing rapidly, or they may go to sleep. On cooling, they at once become more vigorous and perform active movements in their cage. The same effects of changes in the external temperature are familiar in ourselves. The slackness and extreme disinclination to violent exercise experienced in hot moist weather, contrasted with the stringing up of the tone of the muscles which follows exposure to cold, and which may be associated with voluntary exercise to keep ourselves warm, are indications of the important part played by the muscles in determining the heat production of the body. As a rule, the immersion of a man in a cold bath for a minute or two considerably increases his oxygen usage. It is possible, however, to sit in a bath, and, by an act of the will, keep all the muscles in a state of relaxation. Under these circumstances the temperature of the body rapidly falls, and with it the rate of metabolism, as judged by the oxygen consumption of the subject.

This process of adjustment of the body temperature by variations in the heat production, so long as it represents the only method, is extravagant of energy directly the difference in temperature between animal and environment attains any considerable degree. In the very perfect adjustment of the temperature which is present in the higher mammals, regulation of the heat loss plays a greater part than regulation of heat production. The economy of adjustment by heat loss is well shown if we compare in echidna and rabbit respectively the percentage alteration in CO₂ production, when the difference in temperature between animal and environment varies from 10° C. to 20° C. This is, for echidna 72 per cent., for other mammals 16 per cent. In echidna, variations in heat loss can be practically neglected, so that the whole work of regulating the body temperature falls on the heat production. As soon as the external temperature falls below a certain degree, the mechanism fails, the animal's temperature falls, and it passes into a state of hibernation.

THE REGULATION OF HEAT LOSS

In all temperate climates, and, in fact, in all climates except under certain exceptional conditions, the temperature of the warm-blooded animal is higher than that of his environment, so that there must be a constant loss of heat from the surface of the body. In the warm-blooded animals in the arctic regions, and in those which have adopted an aquatic existence, the thick layer of fat which underlies the skin protects the active portions of the body, the muscles and internal organs, from excessive loss of heat to the surrounding medium. In most terrestrial animals, the loss of heat is also diminished by fur and feathers with which these animals are clothed, and in ourselves the same office is performed by clothes, which are capable of voluntary graduation to external conditions. The value of these different coverings depends on the fact that air is a very bad conductor of heat. In the case of a naked man, the layer of air immediately in contact with the surface of the body is warmed, becomes lighter, and rises, its place being taken by fresh cold air. Loss of heat is increased by a draught, which quickens the rate at which the layers of air in contact with the surface are renewed. In clothes, it is the air enclosed in the meshes of the garments and between their different layers that plays the greater part in preventing loss of heat. The rapid cooling effect of wet clothes is partly due to the replacement of layers of air by water, which is a much better conductor of heat.

In addition to the loss of heat by *convection*, *i.e.* by warming the layers of air in contact with the body, heat is also lost by *adiation*, *i.e.* by an exchange of heat between the surface of the body and that of surrounding cooler objects. This loss is also prevented by clothing. Since the material of which clothes are made does not allow the passage of radiant heat, they absorb the heat leaving the body and become warm. This warm article of clothing may in its turn act as a centre for the loss of radiant heat, which may again be prevented by putting on another layer. It is a familiar experience that a multiplication of garments is more effective in retaining the heat of the body than merely increasing the thickness of the individual garments. The rate of loss of heat by radiation is diminished by a rise of the amount of watery vapour in the air, since this makes the air more opaque to the passage of radiant energy. Since the loss of heat depends on the difference of temperature between the surface of the body and the surrounding air or objects, it will be largely affected by the temperature of the skin, and therefore by the amount of blood flowing through the skin. The blood flow through the skin is under the control of the central nervous system, through the vaso-constrictor and vaso-dilator nerves, and it is by altering the size of the cutaneous vessels that the central nervous system chiefly acts in regulating heat loss. In cold weather, or when the heat production in the body is low, the vessels are constricted, the skin is cold, and the heat loss is small. On the other hand, if the temperature of the surrounding air is high, or a large amount of heat is being produced in consequence of muscular exercise, the vessels are dilated and the skin is hot. In hot weather, the dilatation in the cutaneous vessels is associated with muscular inactivity, so that there is a redistribution from the muscles, where the blood is not required, to the skin, where a considerable circulation is necessary.

Loss of heat by radiation and convection can happen only when the temperature of the surrounding air is lower than that of the body. The body temperature can, however, be maintained at its normal height in an atmosphere with a temperature much higher than 37.0°C ., and this in spite of the fact that the production of heat in the body is still going on. This is because there is a profuse secretion of sweat on the surface of the body. In the evaporation of the sweat, especially if aided by a draught of air, a large amount of heat becomes latent and is abstracted from the body, which is therefore kept at a temperature below that of the surrounding atmosphere. If the secretion of sweat is checked by depriving an animal or man of water, or if its evaporation be impeded by placing him in an atmosphere already saturated with aqueous vapour, the temperature of the body runs up rapidly and death ensues from hyperpyrexia or heat-stroke. Although a man can stand exposure to a temperature of 200° or even 250°F . for a considerable time, provided that the air is dry, a temperature of 89°F . is rapidly fatal if the air be saturated with moisture. The same mechanism comes into play when the heat production in the body is very largely increased, as by violent exercise. Under these conditions, a man may sweat profusely when the temperature of the surrounding atmosphere is at 0°C .

The main regulation of heat loss thus takes place by the control, through the nervous system, over the cutaneous circulation and the sweat glands. Besides these channels of heat loss, others may play an important part under certain conditions. Heat is lost to the body in warming the food and air which are taken in. It is also lost in respiration in the evaporation of water and the setting free of CO_2 from watery solution into the expired air.

The following estimate by Tigerstedt represents the proportion of losses in an adult man by these different ways :

A. WARMING THE FOOD AND AIR

(1) 1500 g. water drunk at 15° C. and warmed to 37·7°—raised therefore 22·5°	Cal.
(2) 1500 g. food eaten at 25° C. (mean) and warmed to 37·5°—raised therefore 12·5 ; specific heat 0·8	= 33·75
(3) 15,000 g. (= 11,500 l.) air respired at 15° C. and warmed to 37·5°—raised therefore 22·5° ; specific heat 0·237	= 15·00
	= 79·95
	128·70

B. LOSS OF WATER AND CO₂ IN THE BREATH

(4) It is assumed that the inspired air is half saturated with water vapour at 15° C. and that the expired air is fully saturated at 37·5° C. Approximately 450 g. of water would be given off therefore in the form of vapour from the respiratory passages ; the latent heat of the water vapour is 0·537 Cal.	= 241·70
(5) The absorption of heat in the liberation of CO ₂ from the lungs (800 g.) ; 0·134 Cal. per g.	= 107·20
	348·90
From above	128·70
	477·60
Total	

The sum of heat losses specified under these five headings amounts to 477·60 Cal. Estimating the total heat loss of an adult man at 2400 Cal., this sum represents only about 20 per cent. of the total. The remaining 80 per cent. (in round numbers) takes place through the skin.

If we estimate the total heat loss of an adult man at 2400 Calories, we may say that about 5 per cent. of the total heat loss takes place by warming the food and air, about 15 per cent. by the evaporation of water and CO₂ in respiration, and about 80 per cent. by radiation and convection and the evaporation of sweat from the skin. The proportion represented by the last factor will increase very largely in the presence of a high external temperature, or of an excessive heat production in consequence of violent muscular exercise.

Influence of Atmospheric Conditions.—The cooling power of the air upon the skin varies over an extremely wide range, since it depends upon differences of temperature, humidity, and rate of movement of the air. There is further the influence of the absorption of radiant heat from without, by skin or clothing.

The conditions indoors and outdoors, are, under ordinary circumstances, fundamentally different, the cooling and evaporative powers being greatly reduced indoors, owing to the stillness of the air.

The ordinary thermometer gives us no indication of the physiological aspects of the atmospheric conditions. The wet and dry bulb thermometer gives a little more information, because the evaporative power of the atmosphere is indicated by the depression of the wet bulb instrument. A still better and very practical instrument is the Kata-thermometer (see Fig. 520) introduced by Leonard Hill. This measures the cooling power of the air on surfaces, wet or dry, at body temperature. It is an alcohol thermometer with a large bulb and a stem graduated at 95° and 100° F. It is warmed up to about 105°, and then the time taken to cool from 100° F. to 95° F. is noted. Each instrument is previously calibrated and a numerical factor supplied with it. This factor, divided by the time in seconds taken to cool over the specified range, gives the rate of cooling in micro-calories per square centi-

metre of surface per second. This varies according to the temperature, humidity and velocity of movement of the air. The dry Kata-thermometer gives us the heat lost by radiation, conduction and convection. The wet Kata-thermometer, in which the bulb is covered with a wetted cotton glove, gives us, in addition, the heat lost by evaporation. With this instrument, valuable investigations on the physiological aspects of climatic conditions, and of the influence of clothing on the cooling rates of surfaces, comparable with that of the body, have been made.

THE NERVOUS MECHANISM FOR HEAT REGULATION

The accurate balance between heat production and heat loss, which is responsible for the nearly constant temperature of man, indicates the active co-operation of the central nervous system in every step of the process. Whether this function of temperature regulation can be specially localised in any part of the central nervous system, so that it would be possible to speak of a heat centre, in the same way as we speak of a respiratory or vaso-motor centre, is doubtful. Many observers have found that injury to the *corpus striatum* causes a rise of temperature, associated with increase both in heat production and in heat loss. On the other hand, injury to, or pathological lesions of, the pons Varolii often lead to an increased production of heat in the body, which is not sufficiently compensated for by heat loss, and so causes death by hyperpyrexia. It has been suggested that the *thermogenic* centre, *i.e.* that responsible for regulating heat *production*, is situated at a lower level in the nervous system than the *thermotaxic* system, *i.e.* that which presides over and determines the *balance* between heat production and heat loss. The observations of Meyer and Barbour, that local cooling of the corpus striatum causes increased respiratory exchange and heat production, while warming has the reverse effect, certainly point to a localisation of the thermotaxic centre in this part of the central nervous system. On the other hand, Magnus finds that the body temperature is perfectly regulated if the optic thalamus be intact, all higher parts of the brain, including the corpus striatum, having been removed. Destruction of the optic thalamus, or section of the brain stem just behind the optic thalamus, destroys the animal's power of regulating its temperature. The centres for heat loss must be placed in the medulla, at any rate so far as concerns control of heat loss by alterations in the blood supply to the skin or by the secretion of sweat.

In many warm-blooded animals, the ability to maintain a constant

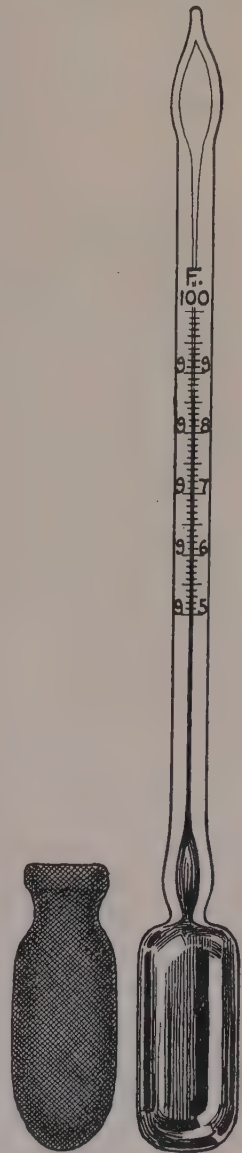


FIG. 520. The Kata-thermometer. On the left the cotton glove for use as a wet indicator. (After L. HILL.)

temperature is not fully developed until some time after birth. Pembrey has shown that, in the guinea-pig and chick, in which the nervous system is fully functional at birth, the heat-regulating mechanism is also completely adequate, whereas animals such as rats, pigeons, or the human child, which are born in a helpless condition, only acquire the power of regulating their own temperature some time after birth. As we should expect, the development of the power of regulating heat production runs *pari passu* with the acquisition of control by the nervous system over the muscles of the body.

CHAPTER XLIII

THE ENDOCRINE ORGANS

AMONG the stimuli which, coming from a distance, evoke the reaction of unicellular organisms, probably the most important are chemical. These reactions are classed together under the term chemiotaxis. When the cells are united to form cell colonies or when, as in the metazoa, the multicellular aggregate is formed by the failure of the products of division of the ovum to separate one from another, the interrelations between the different cells of the organism are still largely determined by chemical stimuli. In fact, in the lowest metazoa such as the sponge, we know of no other means of correlating the reactions of different parts of the cell aggregate. The same chemical sensibility determines the aggregation of phagocytes around bacteria or dead tissue, which forms the essential feature of the process of inflammation in higher animals.

When the reaction of distant parts of the body to a change occurring in any one part depends on the diffusion of some substance from the stimulated part, the total reaction must require a considerable time for its full development. A much more effective method of correlation was acquired by the evolution of a nervous system, by means of which the *consensus partium* could be maintained by the rapid propagation of molecular changes along differentiated paths in the protoplasm. The development of this second mode of correlation of activities did not, however, do away with the necessity for the more primitive method. Even in the higher animals, when rapidity of reaction is not required, we find adaptations carried out in response to some change in distant parts of the body, the message having been chemical and not nervous in character (*e.g.* the secretin mechanism for pancreatic secretion).

When we speak of the chemical correlation of the activities of the different parts of the body, it is important not to confuse processes which have little or nothing in common. In one sense, we may say that every cell in the body is chemically connected with, and dependent on, all the other cells in the body. This interdependence is a necessary consequence of the differentiation of function associated with increased complexity of the organism. Thus, the foodstuffs are digested and absorbed by the cells lining the alimentary canal and are then transmitted, more or less changed by these cells, to all the other tissues of the body. The liver stores up glycogen, and is ready to give of its store to any tissue in need of carbohydrate. The same organ produces urea which passes to the kidneys and is there excreted. All tissues produce carbon dioxide which passes to the lungs to be eliminated, but as it traverses the respiratory centre it arouses respiratory movements, which are exactly proportioned to the tension of the carbon dioxide and therefore to the need of the whole body to get rid of this waste product. The liver converts ammonia into urea, thus shielding all the other tissues from the poisonous effects which would be produced by the entrance of the ammonia into the general circulation. Thus, one organ may receive and modify any substance or foodstuff so as to prepare it for more ready assimilation by other

tissues. It may shield other tissues from the poisonous effects of certain waste products, either by converting them into harmless substances or by excreting them from the body. In all these cases the tissues are dealing with some substance which is utilised in bulk or which, by its accumulation, could exert a toxic influence on other tissues. We are probably justified in treating apart a group of phenomena in which the substance transmitted from one part of the organism to another is significant almost entirely as an excitatory agent, and has little or no value as a source of energy. When the adaptation to a change of A consists in increase or diminution in the activity of an organ B, the change in B can be evoked either by a nerve impulse passing from A to the central nervous system and from this to B, or by the production at A, as a direct consequence of the stimulus, of a specific chemical substance, which passes into the circulating blood to B, where in its turn it will produce the required state of action. Such chemical messengers are designated *hormones*, from ὁρμάω, 'I excite.' We have already met with several examples of such bodies. It may be interesting here to consider what must be their general character if they are to fulfil the part of chemical messengers.

(1) In the first place, they must not be *antigens*, *i.e.* their injection into the blood stream must not involve the production of an antibody. If this were the case, the hormone, on entering the blood stream, would meet its antibody and would be unable to exert any effect on the appropriate reacting organ. The hormones must be simpler in character than such substances, and, actually, most of them have a precise and comparatively simple chemical and molecular constitution.

(2) Since they must be carried by the blood stream to the reacting organ, they must, in most cases, be susceptible of easy passage through the walls of the blood vessels, if they are to excite a reaction within a fairly short space of time. This consideration would also tend to keep their molecular weight comparatively low.

(3) As a rule, the chemical messenger must excite a state of activity (or of inhibition) in response to a change in some other part of the body. When the primary change passes away, the action of the hormone should also disappear. On this account it is necessary that the hormone should either be susceptible of easy destruction, by oxidation or otherwise, in the fluids of the body, or be readily excreted, so that its action may not be continued indefinitely.

In previous chapters, we have already come across several examples of correlated activities of different tissues, effected by chemical means. In the alimentary canal, the secretion of pancreatic juice, at the precise moment when it is required in the duodenum for the digestion of the food arriving there from the stomach, is evoked by the production in the cells of the intestinal mucous membrane, under the agency of the acid of the gastric juice (the specific stimulus), of a substance, *secretin*. This substance, which is heat stable and diffusible but is easily destroyed by oxidation, is absorbed into the blood and carried to the pancreas, where it acts as a specific stimulus for the secretory cells. This is perhaps the best example of a chemical reflex, *i.e.* an adaptation effected by chemical means rather than by impulses passing along the nerve channels. There are, however, many other examples of a chemical influence exerted by one organ on another, in which the interaction probably depends on the production of minute quantities of some substance acting in virtue of its excitatory qualities, rather than of its value as a source of energy.

For many of the organs of the body we know, in fact, no other function than the production of some substance, the presence of which in the blood is a necessary condition for the carrying out of the normal func-

tions either of growth or activity of many other parts of the body. In other cases, an organ may have a twofold function. Thus, the pancreas gives an external secretion, which is used for the preparation of the food for absorption, and an internal secretion which, passing into the blood, exercises an important influence on the metabolism of the foodstuffs after absorption. Other instances of these chemical correlations may be cited. The secretion of gastric juice, which results from the presence of peptones or other substances in the stomach, has been ascribed by Edkins to the production, in the pyloric mucous membrane, of a gastric hormone. According to Frouin, the injection of boiled succus entericus, free from secretin, provokes the secretion of intestinal juice. In the reproductive system, we have many examples of such chemical correlations. All these examples are discussed in fuller detail in other parts of this book. There is one class of organs in which a chemical influence, exerted by them on the rest of the body, is the only function with which we are acquainted. These are included under the terms *endocrine organs* or *ductless glands*. As examples, we may cite the suprarenal bodies, the thyroid and parathyroids and the pituitary body.

METHODS OF INVESTIGATION.—The investigation of the functions of the endocrine organs consists essentially in studying the effects on the various functions of the body, of augmenting and of diminishing the amount of active principle of the organ in question. There are several directions along which this information may be obtained. Thus, in certain diseases, the endocrine organ in question produces less of the active principle than it does in the normal state, or, conversely, in conditions associated with overgrowth of the gland, it may produce more.

The effects of lack of the endocrine principle can be studied in experiments on animals, by the removal by operation of the gland in question, such operations being, where possible, performed in a series of stages, so that the resultant change is a gradual one. Then, having produced the effects of lack of the active substance, we may attempt to make good this lack by the administration of the substance, either by feeding with the gland, by administering extracts of it intravenously or subcutaneously, or by the surgical grafting of a portion of the gland from another animal of the same species. We can also, of course, study the effects of such administration of the active principle to the normal animal or man, and thus learn the physiological effects of an excess of the hormone.

The presence, in extracts of tissues, of substances which exert definite physiological effects when administered in appropriate ways, is, however, no proof that the organ in question normally produces that substance for the benefit of the whole body, or that the substance is ever passed, as such, from the organ into the blood or lymph. Strict proof would require evidence that the organ in question, (*a*) contained an active chemical substance, which (*b*) is essential to some other parts of the body, so that (*c*) definite effects would ensue, if the tissue which forms this active principle were all removed, but (*d*) these effects would disappear if the active principle was suitably administered; (*e*) the active substance should be demonstrable in the blood or in the lymph leaving the organ in which it is produced.

Finally, chemical investigation seeks to ascertain the nature of these active principles, with the view to their ultimate synthesis in the laboratory, an end which has already been achieved in two instances.

THE SUPRARENAL BODIES

The suprarenal capsules, or adrenals, in mammals are two small masses lying on the upper or oral side of the kidneys. They consist of two parts, the cortex and the medulla.

The cortex is composed of cells arranged in columns or in a reticular fashion. The outermost layer of cells often presents an alveolar structure, the lumen, however, being but little marked. According to the arrangement of its cells the cortex is divided into three zones, the zona glomerulosa, zona fasciculata, and zona reticularis. The cells themselves are distinguished by the large amount of granules they contain, which give the ordinary reactions for fat but consist probably of lecithin compounds. In some animals, *e.g.* the guinea-pig, the cells, especially towards the inner part of the cortex, contain many yellow pigment granules. In the portions of the cortex adjoining the medulla are numerous fine granules staining black with osmic acid, but insoluble in turpentine (CRAMER).

The medulla, much less extensive than the cortex, presents irregularly shaped cells, the outlines of which are but slightly marked. These cells contain granules which stain darkly with chromates and give a green colour with salts of iron. It is hence easy to delimit the area of the cortex in any section of a gland which has been hardened in a fluid containing chromates. The substance giving this reaction is known as chromophile or chromaffine substance. The fine osmic-staining granules are also present in abundance in these cells. The suprarenals are richly supplied with blood, especially in the medullary part, the cells of which impinge directly on the endothelial lining of dilated capillaries. They also receive an abundant nerve supply from the sympathetic system (splanchnics), the nerves forming a thick meshwork, especially in the medulla, and presenting at intervals ganglion cells, which may either be isolated, or combined to form small ganglia.

A study of the development of the suprarenal glands shows that we have here to do with two distinct tissues, probably differing in the part they play in the animal economy. Whereas the cortex is derived from that portion of the mesoblast, the 'intermediate cell mass,' from which the mesonephros is also developed, the medulla is produced by an outgrowth from the sympathetic system, and may indeed be said to consist of profoundly modified nerve cells. In many fishes, these two elements of the suprarenal gland remain separated throughout life, the cortex being represented by a series of paired interrenal bodies lying on the front of the spinal column, and the medulla by a number of collections of chromaffine cells, lying in close juxtaposition to the spinal nerves.

In some animals, accessory suprarenals are not infrequent in which both cortex and medulla may be represented. In all animals we find masses of tissue, the so-called paraganglia, in close association with the sympathetic system, which present the chromaffine reaction typical of the medulla. Since a watery extract or decoction of these bodies has the same influence, on injection into the blood stream, as an infusion of the medulla of the suprarenal body itself, we are probably justified in regarding these bodies as equivalent to accessory medullary portions of the suprarenal. They have the same origin, the same staining reactions, and the same physiological effect as the latter.

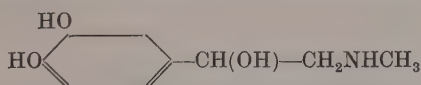
Scattered portions of cortical tissue are also found in many animals, usually near to the gonads.

Addison in 1855 drew attention to the coincidence of degenerative destruction of the suprarenals with a disease which since that time has been known as Addison's disease. The three cardinal symptoms of this disorder are (1) bronzing of the skin, (2) vomiting, (3) excessive muscular weakness and prostration. The disease is almost invariably fatal. Addison's observations have been amply confirmed since that time, but we are not yet in a position to account for the occurrence of all these symptoms as a result of interference with the cortex and medulla of the suprarenals. The experimental destruction or extirpation of these bodies has naturally been frequently carried out, but it has been impossible to reproduce the bronzing which is so characteristic of Addison's disease. The one symptom which is observed as a result of the experimental extirpation is the excessive prostration, which is attended with muscular weakness and a lowered blood pressure and body temperature. Extirpation of one suprarenal has no effect beyond that of sometimes leading to hypertrophy, especially of the cortex, of the other one. The results of extirpation of both suprarenals varies. It is easy to keep rats alive after total extirpation of these organs, and many rabbits also survive double epinephrectomy indefinitely. To cats, dogs and guinea-pigs, however, the operation is fatal in, at most, a few days. When extirpation

is fatal, death occurs suddenly, and is preceded by rapid decline, collapse, and a shock-like condition, with great concentration of the blood. This state of collapse can be evoked very easily in an epinephrectomised animal by the administration of a small dose of histamine, to which such animals are abnormally sensitive.

It seems practically certain that the rapidly fatal effect of extirpation of both suprarenals is to be ascribed rather to the removal of the cortex than of the medulla. The medulla can be destroyed by operation, or by insertion of a small tube of radium, without causing death. It seems that the functions of the medulla, if essential to life, can be more or less effectively maintained by the other chromaffine tissues found at the back of the abdomen. But there is no conclusive evidence that the chromaffine material is essential to life. In the cases where animals survive double extirpation, small masses of accessory cortical substance have been found embedded in the kidney or elsewhere in the neighbourhood of the suprarenals or gonads. Hypertrophy, or a tumour of the suprarenal cortex, in children is associated with premature sexual maturity. It is possible that future work may show some connection between the cortex and the destruction of pigment in the body. At present it is only by a process of exclusion that we may guess at a causal relationship between the destruction of the cortex and the bronzing which occurs in Addison's disease. There are indications that the cortex plays some part in cholesterol metabolism. The evidence as to the functions of the suprarenal cortex is so scanty and conflicting, that it would not be profitable to discuss it any further.

The evidence regarding the medulla is more satisfactory. Schafer and Oliver in 1894 found that a watery extract of the suprarenal bodies, when injected into the circulation, caused a great rise of blood pressure, brought about chiefly by constriction of all the blood vessels of the body. The active substance responsible for this rise was limited to the medulla, infusions of the cortex being without influence. Later on, Abel studied, and Takamine isolated, the active substance, to which the name of *adrenaline* was given, and since that time the synthesis of adrenaline has been effected. Adrenaline gives a blue colour with phosphotungstic acid, a reaction which can be employed for its quantitative estimation (Cannon, Folin and Denis). The constitution of adrenaline is shown by the following formula:



Both dextro- and lævo- forms, as well as the racemic modification, have been prepared synthetically. The substance which occurs in the suprarenal gland is lævorotatory, and Cushny has shown that the dextrorotatory compound has only one-twelfth the physiological effect of the lævorotatory. Adrenaline is active in excessively minute doses, injection of one four-hundredth of a milligramme per kilo body weight sufficing to evoke a definite rise of blood pressure. On injecting it into the circulation there is immediately a rise of blood pressure which, if the vagi are intact, is only moderate in amount, since it is accompanied by a marked slowing of the heart. This excitation of the vagus is, however, probably secondary to the rise of blood pressure, and is not due to direct action of the drug on the vagus centre. If the vagi be divided, the injection of adrenaline evokes a huge rise of pressure, which may amount to 300 mm. Hg. It may, indeed, be so great that the animal dies from heart failure or from pulmonary oedema. The rise of pressure is observed even after destruction of the central nervous system.

The action is not limited to the blood vessels. It has been shown by Langley and by Elliott that adrenaline injected into the circulation arouses every activity which can be normally excited by stimulation of the sympathetic system. A list of the actions of adrenaline is therefore identical with a list of the chief functions of the sympathetic nervous system. When a dose of adrenaline is injected, the liver glycogen is rapidly discharged, and hyperglycæmia and glycosuria result. The heat production and oxygen usage are increased. In the head, it causes dilatation of the pupil, secretion of saliva, and erection of the hairs. The dilatation of the pupil takes place much more readily after previous removal of its sympathetic supply by excision of the superior cervical ganglion. Such a 'denervated' pupil will respond to a dose of adrenaline which is much too small to affect the normal one. On the heart it has a strong augmentor and accelerator influence, so that this organ beats more effectively as a rule, even against the enormously increased resistance offered by the constricted arterioles. Whereas a rise of blood pressure generally causes increased systolic volume of the heart, we may find after an injection of adrenaline, and during the height of the rise of blood pressure, that the heart empties itself more effectively than it did before the injection. The bronchi and bronchioles are fully relaxed; respiratory movements are often temporarily inhibited (adrenaline apnoea). On the lung vessels, adrenaline has probably a slight constrictor influence. With regard to the vessels of the brain, we find the same divergence of opinion as in the case of excitation of possible vaso-motor nerves to this organ. In the abdomen, intravenous injection of adrenaline causes complete relaxation of the musculature of the cat's and the human uterus, of the stomach, and of the small and large intestines, but contraction of the ileocolic sphincter, and of the rabbit's uterus. On the bladder, its effect varies according to the animal studied, but in every case is identical with that obtained by stimulating the hypogastric nerves. It has been shown by Dale that adrenaline may also excite vaso-dilator fibres or produce vasodilator effects, when such effects are also obtained from stimulation of the sympathetic nerves. In fact, very small doses of adrenaline usually cause a definite fall of blood pressure in anæsthetised animals. The motor effects of adrenaline are usually reversed after previous injection of ergotoxin, the active alkaloid of ergot. This drug, when injected, causes, first, active vasoconstriction and rise of blood pressure, followed by paralysis of the vasoconstrictor mechanism. Excitation of the splanchnic nerves, or injection of adrenaline, will now bring about a fall of blood pressure, due to dilatation of the vessels in the splanchnic area.

The point of attack of the adrenaline appears to be in the muscular or glandular tissues themselves, since its effects may not only be obtained after destruction of the cord and sympathetic plexuses, but even obtained (and in an exaggerated degree) after time has been allowed for the peripheral (post-ganglionic) fibres to degenerate as a result of extirpation of the corresponding ganglia. Although, under these circumstances, the effect is not lessened, and adrenaline may still produce either relaxation or contraction of muscles, according to the original action of the sympathetic on these fibres, we may perhaps assume with Langley and Elliott that the action of adrenaline is on some substance mediating between the nerve and the responsive tissue.

Each suprarenal receives a number of filaments from the splanchnic nerve on its own side. These pass to the medulla, where they end apparently without the interposition of any ganglion cells on their course (Elliott), the cells of the medulla having themselves been developed by a modification of sympathetic ganglion cells. Stimulation of the peripheral end of the

splanchnic nerve causes, as we have already seen, a discharge of adrenaline into the blood stream. This discharge accounts for the secondary rise, often accompanied with quickening of the heart, observed on a blood-pressure tracing as the result of stimulating the splanchnic nerve. Through the splanchnic nerves, a discharge of adrenaline can be excited by many general conditions, such as anoxæmia, pressure on the brain, puncture of the fourth ventricle, administration of anæsthetics, or mental disturbances such as excitement or fright. Such a discharge is an important element in the adaptation to environmental stress, and enables the animal to react for the preservation of its life either by offence or by flight. If one splanchnic nerve be cut before the administration of anæsthetics or the induction of a condition of irritation or fright, the suprarenal gland on the corresponding side will be found to contain two or three times as much adrenaline as the gland which has been left in connection with the central nervous system. It is interesting that no such condition of exhaustion can be produced by electrical stimulation of the peripheral end of the divided splanchnic.

Cannon and his co-workers have demonstrated the liberation of adrenaline from the suprarenals, by observing the acceleration of the denervated heart. Cats were used in these experiments, and the heart was denervated by removal of the stellate and other thoracic sympathetic ganglia and section of the vagi in the neck. Such animals in states of asphyxia, fear, pain or rage showed pronounced cardiac acceleration, but if the splanchnics were divided, the effect was very slight or absent. Reflex secretion of adrenaline could also be shown in this preparation by stimulation of the central end of the sciatic nerve.

Similarly, Kellaway, using a cat with the pupil of one eye deprived of its sympathetic supply, has shown that the hypersensitive denervated pupil dilates in even mild degrees of asphyxia or oxygen lack.

Tournade and Chabrol have also shown that the secretion of adrenaline may be produced reflexly. Their method is to anastomose the suprarenal vein of one dog A, with the external jugular vein of a second dog B. The arterial pressure of B is recorded and the spleen of B placed in a plethysmograph. When the central end of the sciatic nerve of A was stimulated, there was a rise of blood pressure and a shrinkage of the spleen in B. By a similar technique, Heymans has shown that a fall of blood pressure in the arteries of A (but especially in the *sinus caroticus*) leads to a reflex liberation of adrenaline.

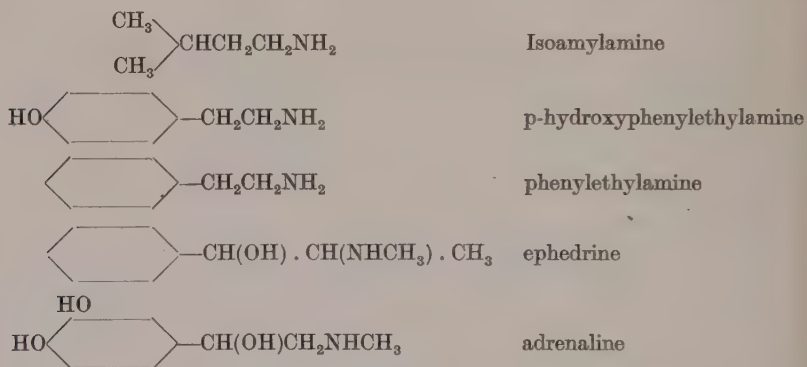
Stewart and Rogoff, using other methods, claim to have demonstrated that adrenaline is continually being passed out from the suprarenals into the blood, and that although an increased output is demonstrable on stimulation of the splanchnics, no such increase can be obtained reflexly.

When adrenaline is injected into the blood stream, the effect is only temporary. It is not excreted in the urine, but rapidly disappears from the blood. Since it is easily oxidised, and is extremely unstable in alkaline solution, we may conclude that, after performing its excitatory function, it is destroyed by oxidation in the fluids. Adrenaline is thus a typical hormone, a body of comparatively low molecular weight, having a drug-like excitatory action on specific tissues of the body, easily diffusible, and rapidly destroyed after discharging its office.

There seems little doubt that we must regard adrenaline as a true internal secretion, and must ascribe to the medulla of the suprarenal capsules and to the other chromaffine tissue in the body the function of elaborating this substance. What part it plays in the normal functions of the body has, however, been contested with no little heat. Whether adrenaline is continuously discharged into the circulating blood, and, if so, in what amounts and with what, if any, consequences, and whether or not the rate of liberation is augmented by emotion, asphyxia, splanchnic stimulation, fall of blood-sugar, etc., have been the principal subjects of controversy. The bulk of opinion seems to be that adrenaline is very slowly poured out by the normal

suprarenal, and that this output is stopped or greatly reduced by section of the splanchnic nerve supply; that the amount of adrenaline so liberated is too small to exert an effect upon the tone of the arterioles, though it might affect the tone and permeability of the capillaries; and that, in states of emotion, asphyxia, exposure to cold, etc., there is a sudden liberation of adrenaline in such amount as suffices to produce the effects seen on injection of that substance into the blood stream. According to this view, we should be inclined to regard the suprarenal medulla as not essential to life, but as a useful adjunct in times of stress.

Owing to the rapid destruction of adrenaline, it produces little if any effect when given by the mouth. There is, however, a whole series of substances, more or less allied to adrenaline in chemical constitution, which undergo less rapid destruction and can therefore be administered as drugs in the usual way. Dale and Barger have described three such substances as occurring in infusions of ergot. Another similar substance is the drug ephedrine. The constitution of these substances is shown in the following formulæ:



The formula of adrenaline is placed below, in order to show the relation of these substances to the natural hormone. These bodies are produced from the amino-acids of proteins by a process of decarboxylation. Leucine would yield isoamylamine, tyrosine hydroxyphenylethylamine, and phenylalanine would give phenylethylamine. Such substances may be formed in minute quantities during the normal processes of putrefaction which occur in the alimentary canal.

THE THYROID GLAND

The thyroid gland consists of two oval bodies lying on either side of the trachea, and joined, in many animals, across the trachea by an isthmus. Surrounded by a capsule of connective tissue, it is made up of an aggregation of vesicles varying in diameter from 15 to 150 μ . The vesicles are lined by a single layer of cubical epithelial cells, and are filled with a translucent material known as colloid (Fig. 521). Of the cells, some present granules and resemble the cells of a secreting gland, while others contain masses of colloid, or have undergone colloidal degeneration. Mitochondria are sometimes very abundant in the cells, and these and the Golgi apparatus undergo definite changes under conditions which are believed to be associated with alterations in the secretory activity of the thyroid, *e.g.* an increase when the animal is exposed to cold. Between the vesicles may be seen, here and there, solid masses of cells which by some observers are regarded as destined to replace vesicles the epithelium of which has undergone complete degeneration. Since the gland possesses no duct, it is supposed that the cells furnish an internal secretion, which makes its way into the blood along the lymphatic efferents of the gland. The thyroid is richly supplied with blood by the superior, middle, and inferior thyroid arteries, and is surrounded with a plexus of veins lying immediately under the capsule. In development, the thyroid is formed by a downgrowth from the floor of the pharynx, the site of which is subsequently marked by the *foramen cæcum*, but the connection with the mouth disappears early in fetal life. In rare cases part of the thyroglossal duct may

persist and, becoming gradually filled with fluid, give rise to a cyst which lies below the tongue and may require excision by the surgeon.

As with the other endocrine organs, clinical observations have contributed materially to our knowledge of the functions of the thyroid. In this country, attention was called to the connection of a disturbed condition of metabolism known as *myxœdema* with alteration or atrophy of the thyroid. A patient affected with myxœdema presents a gradually increasing blunting of his or her mental activities; speech is slow, cerebration delayed. With this nervous defect are associated changes in the connective tissues, the subcutaneous connective tissue becoming thickened, so that the face and hands appear swollen and puffy, looking at first sight as if œdema were present. The swelling is, however, due to newly-formed connective tissue, and not to the presence of an excess of interstitial fluid in the tissues. The patient often has a yellow waxy appearance, with a patch of colour on the cheeks. The hair falls out, the pulse is slowed, and the temperature tends to be subnormal owing to the diminution of the rate of metabolism in the body. Determination of the patient's basal metabolic rate shows this to be definitely below the normal value, as calculated from weight and height. The intake of food and the excretion of urea are diminished.

If the atrophy of the thyroid occurs in early life during the period of growth, *e.g.* in young children, the growth of the skeleton practically ceases. The bones of the limbs may grow in thickness but not in length. There is early synostosis of the bones of the skull, and complete cessation of development of mental powers. Children so affected are called *Cretins*. They may live for many years, but when twenty-five or thirty present still a childish appearance (Fig. 522, c). Stunted, pot-bellied and ugly, they have the intelligence of children of four or five. They often present fatty tumours above each clavicle, and similar subcutaneous tumours of fat or loose fibrous tissue are found in cases of myxœdema in the adult.

Removal of the thyroid from tadpoles causes a comparable failure of proper development, so that metamorphosis is absent or delayed. When the thyroid is extirpated in man the result is often the production of typical myxœdema. In some early cases a condition of tetany was observed after the operation, characterised by tonic spasms of the muscles of the body especially of the extremities, and this was also a frequent result of extirpation of the thyroid in animals. But there is now no doubt that this condition was due, not to removal of the thyroid itself, but to the fact that the parathyroids were taken away at the same time. If care be taken to spare the parathyroids at the operation, removal of the thyroid from young animals, as Sutherland Simpson has shown, results in the same retarded development and stunting of growth as are observed in human beings when there is atrophy of the thyroid gland alone.

Many authorities were at first inclined to explain these results in man and animals on the hypothesis that there was normally a destruction of toxic

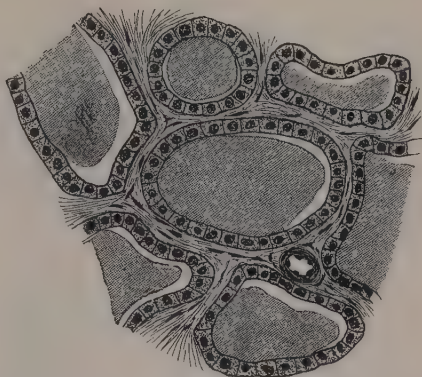


FIG. 521. Section of Thyroid Gland of Dog.
(SWALE VINCENT.)

substances by the thyroid gland. This theory is put out of court by the results of administration of thyroid gland to patients with myxœdema, or to animals deprived of their thyroids.

Schiff first showed that the effects of extirpation of the thyroid might be prevented if, at the same time, the thyroid from another animal were transplanted into the subcutaneous tissue, to take the place of the one removed. On removing the transplanted thyroid, the typical symptoms of thyroid deprivation at once ensued. It was later found that similar good results could be obtained by subcutaneous injection of the expressed juice of the thyroid, and afterwards that it was sufficient to administer the thyroid gland, either fresh, dried, or partially cooked, by the mouth. An ugly and idiotic cretin can be converted by this means into a child of ordinary intelligence with normal powers of growth (Fig. 522 A and B). Given to myxœdematous patients, the



FIG. 522. A. A cretin, 23 months old. B. The same child, 34 months old, after administration of sheep's thyroids for 11 months. C. A cretin, untreated, 15 years old. (W. OSLER.)

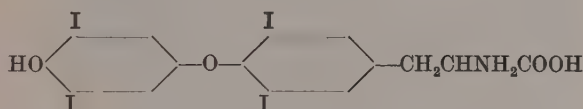
thyroid gland restores the basal metabolism to its normal level, reduces the swelling of the subcutaneous tissues, causes a new growth of hair, and reinstates the patient's former condition of mental health. It is possible that a moderate degree of thyroid inadequacy is not infrequent, and that the beneficial effects on general health, in removing excessive corpulence and in promoting the growth of hair, which are observed on administering the drug to people of middle life, may be due to the actual reinforcement of a function which is being insufficiently discharged. Nor is the thyroid gland without influence on the healthy individual. When tadpoles are fed with thyroid substance, the rate of metamorphosis is greatly accelerated. If given in large doses either to man or to animals, it quickens the pulse, even causing violent palpitation, and increases the metabolic activities of the body, so that the appetite is increased, the glycogen store of the liver is reduced, the nitrogenous output rises above the intake, and the subcutaneous fat is diminished or disappears.

The symptoms caused by excessive doses of thyroid gland are strikingly similar to those occurring in the disease known as *exophthalmic goitre*, where there is a true hypertrophy of the gland associated with increased basal metabolic rate, cardiac palpitation, proptosis (bulging of the eyes), wasting, great restlessness, occasional glycosuria, and muscular weakness.

In these cases, removal of the hypertrophied gland, or of the major part of it, removes the symptoms and restores the patient to health. If the whole gland is removed it is necessary to administer daily doses of dried gland for the rest of the patient's life, in order to prevent the development of myxœdema.

All these facts warrant us in including the thyroid body among the glands with an internal secretion, the presence of which in the blood stream is a necessary condition for the normal growth and functions of almost all the tissues of the body. If this secretion is lacking, we obtain the condition known as myxœdema in adults, and as cretinism in young children. If it be present in excess, the symptoms of exophthalmic goitre are produced. There are grounds for the belief that the thyroid plays a part in the production of the increased metabolism and rise of temperature in fevers.

The specific hormone contains iodine in organic combination. Kendall in 1914 isolated an active principle of the thyroid, and gave it the name *thyroxin*. Harington and Barger in 1927 showed this to have the structural formula :



and prepared the compound synthetically. The thyroid of an average human adult probably contains about 20 mg. of thyroxin. This substance when administered, exhibits all the therapeutic properties of the dried gland itself. Thus 1 mg. of thyroxin definitely raises the basal metabolic rate, the maximal effect appearing after a day or two. It also relieves the condition of hypothyroidism, and accelerates the metamorphosis of tadpoles. It is believed that the thyroid of the normal individual produces about 1 mg. thyroxin a day. If iodine be entirely absent from the drinking water and the soil, and hence from the vegetable food grown in the district, the thyroid undergoes hyperplasia—in a vain endeavour to make bricks without straw, to produce its proper hormone without iodine. This seems to be the cause of the great prevalence of goitre in certain inland districts, especially in Switzerland and in parts of the United States. It has been shown by Marine and others that this endemic goitre can be practically eliminated from these districts by the occasional administration of minute doses of iodine or iodides to the entire population (as by addition to the water supply or to the table salt).

Although thyroxin produces effects so similar to those of the gland itself, it is not at all certain that thyroxin, as such, is eliminated by the thyroid, or circulates in the blood. The delay which elapses between the administration of thyroxin, and the production of physiological effects, may mean that the relatively simple molecule of that substance needs to be built up into some more elaborate molecule before it can be effective. The earliest active materials prepared from the thyroid were in fact, globulins, of which perhaps thyroxin formed one of the constituents.

THE PARATHYROIDS

The parathyroids are four small bodies, varying in number, and situated, two on each side, on the border of the thyroid gland or actually embedded in its substance. One of each pair is developed from the 3rd, and one from the 4th branchial pouch. In histological appearance, they consist of solid masses or columns of epithelial cells, surrounded with connective tissue and richly supplied with blood vessels (Fig. 523). In some animals, *e.g.* in the dog, where they are embedded in the gland, they will usually be removed in any operation for the extirpation of the thyroid. In others, such as the rabbit, where they lie outside the gland, it is easy to avoid them in the excision of the thyroid. To this varying distribution of the parathyroids have been

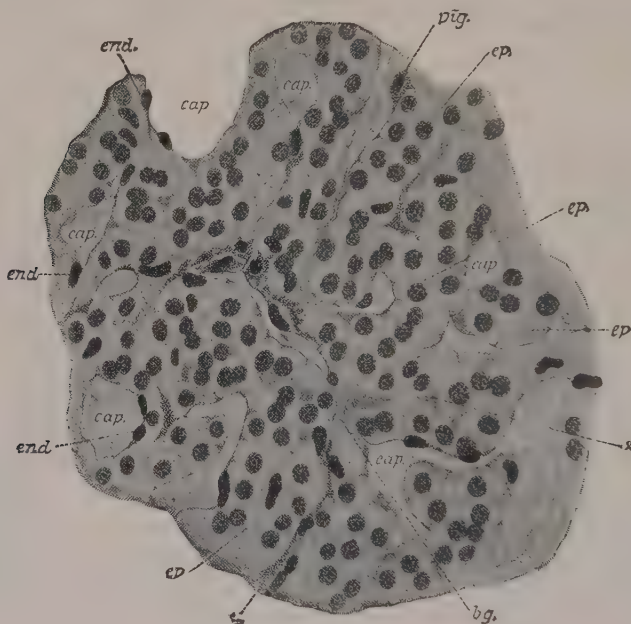


FIG. 523. Section of Parathyroid. (KOHN.)

ep. Secreting epithelium.

pig. Cells containing pigment.

cap. Sinus-like capillaries.

end. Endothelial cells.

ascribed the discrepant early results of extirpation of the thyroid in carnivora and herbivora respectively.

In spite of their close anatomical association with the thyroid, the parathyroids have a function entirely distinct from that of this gland. Whereas removal of the thyroid produces simply a condition of cachexia and the changes associated with myxœdema, or retardation of growth in the young animal, removal of the parathyroids is followed by nervous disturbances and tetany, which may rapidly prove fatal, especially in young animals. This condition is found to be always accompanied by a diminution of the calcium content of the blood, which falls from the normal figure of about 10 milligrammes per 100 c.c. serum to between 4 and 7 milligrammes. The symptoms are found to be temporarily relieved by administration of calcium chloride, either by the mouth or subcutaneously. The condition of tetany after parathyroidectomy may be relieved by subcutaneous implantation of a normal gland.

Collip has shown that, by extraction of fresh parathyroid glands with 5 per cent. hydrochloric acid and then precipitating the proteins by neutralisation, a fluid is obtained which contains the hormone of the parathyroids in a very potent form. One or two injections per day of this fluid serves to ward off indefinitely the symptoms of tetany in parathyroidectomised dogs, or to cure such symptoms when they have already supervened, either in dogs or in human beings suffering from tetany due to parathyroid insufficiency. The parathyroids are thus the seat of formation of a hormone which regulates calcium metabolism through a specific control of blood calcium concentration.

When the extract is administered to normal dogs there is a steady rise in the calcium content of the serum, which reaches a maximum in five to nine hours, and then returns at the same rate to normal. When several successive injections are made, there is a

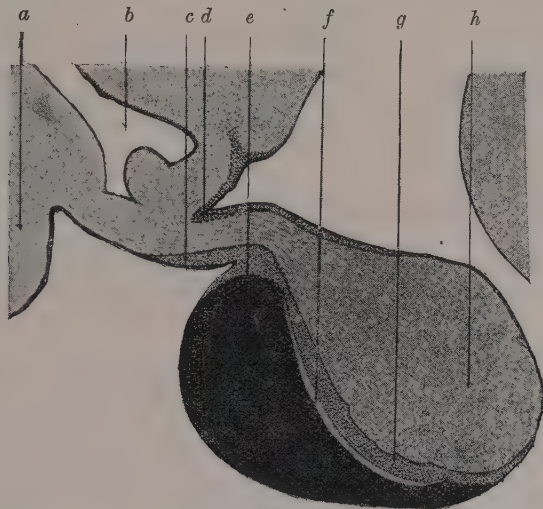


FIG. 524. Mesial Sagittal Section through the Pituitary Body of an Adult Monkey.
(Semi-diagrammatic.) (After HERRING.)

- | | |
|---|----------------------|
| a. Optic chiasma. | e. Anterior lobe. |
| b. Third ventricle. | f. Epithelial cleft. |
| c. Pars tuberalis. | g. Pars intermedia. |
| d. Epithelial investment of posterior lobe. | h. Posterior lobe. |

summation of effect, and the calcium value of the serum may rise to 15 or 20 milligrammes per 100 c.c. When the figure of 15 is passed, the dog shows definite symptoms of 'hypercalcaemia.' The animals become weak, there is diarrhoea and vomiting, followed by collapse and death. The impairment of the circulation is associated with great increase in the viscosity of the blood. As in the case of thyroxin and insulin, pathological conditions and death may be caused by either abnormal deficiency or abnormal excess of the hormone in the body. According to Paton and his associates, the parathyroids are concerned in the removal from the circulation of a toxic substance, guanidine; after removal of the parathyroids this is said to accumulate and give rise to some of the symptoms which ensue.

THE PITUITARY BODY

In the pituitary body we have four important structures, the *anterior lobe*, *posterior lobe*, *pars intermedia*, and the *pars tuberalis*. It is not possible to say with precision where the various active constituents of the gland are formed, or by what paths they reach the blood stream. The pituitary body consists of two main parts, anterior and posterior, which have separate modes of origin. An outgrowth from the buccal cavity in the embryo meets a hollow extension of the anterior cerebral vesicle. The buccal ectoderm gives rise to the anterior lobe and pars intermedia of the pituitary, while the neural epiblast becomes developed into the posterior lobe (Fig. 524). In some animals, the

posterior lobe remains hollow and retains its primitive connection with the third ventricle of the brain, but in man it becomes entirely solid.

The *anterior lobe* in the adult consists of nests of epithelial cells, many of which, the chromophobe cells, are only stained with difficulty, while others are filled with eosinophile or basophile granules. Acini filled with a colloid material are also often seen. The anterior lobe is separated from the posterior lobe by a cleft, which is the remains of the original hollow outgrowth from the buccal cavity. The anterior lobe and *pars tuberalis* are highly vascular, the other parts only poorly supplied with vessels. The epithelial tissue immediately surrounding the cleft probably belongs to the *pars intermedia* and differs from that constituting the anterior lobe. Its cells, which present but few granules, are arranged in islets, separated by an intervening tissue continuous with the main mass of the posterior lobe. Many of the islets are hollow and enclose a colloid material. The colloid material has been traced by Herring into the interalveolar connective tissue and into the prolongation of the infundibulum which enters the posterior lobe. It has therefore been supposed that the active principles of this colloid material, or of the cells which form it, and also that of the posterior lobe, pass directly into the third ventricle. The amount of colloid material increases in animals which have undergone extirpation of the thyroid gland.

The main bulk of the posterior part, the *pars nervosa*, is composed of neuroglial tissue.

The *pars tuberalis* surrounds the infundibular stalk, and spreads out on the base of the brain in the neighbourhood of the tuber cinereum. It is said to be histologically quite different from the *pars intermedia* and anterior lobe. It is much more vascular than the *pars intermedia*, and has an acinar structure; the eosinophile cells characteristic of the anterior lobe are wanting. The interest of the *pars tuberalis* is due to the fact that it has recently been found that most of the results attributed to removal of the pituitary body can be obtained by merely injuring the hypothalamic region; these results are polyuria, glycosuria, loss of heat regulation, and early death.

Our first clue to the importance of this organ in the normal processes of the body was furnished by the observations of Pierre Marie, who found that the morbid condition of *acromegaly* is associated with tumours of the pituitary gland. This disease consists in an increased growth of certain parts of the skeleton, especially the lower jaw and the extremities of the limbs. Headache is often present, and there may be polyuria and limitation of the temporal field of vision. When this disease occurs during the period of active growth, there may be an increase in length both of the limb-bones and of the trunk, and most of the giants which are shown from time to time, are examples of this pathological condition of 'gigantism.' It seems probable that this condition is due to an over-action of the gland. In cases of *acromegaly* the tumour is generally an enlargement of the ordinary gland tissue of the anterior lobe. It has not been possible, by transplantation, to replace a removed pituitary body, since the transplanted organ has hitherto always undergone degeneration. In a certain number of cases, animals, especially if young, have survived extirpation of the pituitary body. In these the operation was followed by arrest of development—the animals remaining in an infantile condition, small, with an excess of fat, and absence of sexual development.

The two lobes, anterior and posterior seem to have entirely different functions. The intermediate epithelial substance is closely adherent to the posterior lobe, and its functions have not been dissociated from that of the latter.

The *anterior lobe* is in some way responsible for the growth of the animal, its hypertrophy leading to gigantism or *acromegaly*, while its removal or degeneration gives rise to the arrested development of the bony skeleton and of the sexual functions already alluded to. The relation of the pituitary body to the sexual functions will be considered in the chapter on Reproduction. Experimental gigantism has been produced in animals by administra-

tion of extracts of the anterior lobe, and feeding of amphibian larvæ with the anterior lobe has been shown to accelerate metamorphosis. Clinically, some beneficial effects have been described as following oral administration of huge doses of the dried gland in certain cases of dyspituitarism. This lobe must be associated in some way with the thyroid gland, since it exhibits hypertrophy if the thyroid has been removed.

Active Principles of the Posterior Lobe, Pars Intermedia and Pars Tuberalis. Extracts made from the pituitary, after removal of the anterior lobe, cause a rise of blood pressure when injected intravenously, and this observation formed the starting point for the investigation of the active principles of the posterior lobe, with its attached parts.

The physiological effects which can be produced by injection of unpurified pituitary 'posterior lobe' extracts are as follows:

- (1) Rise of arterial blood pressure (*pressor* action).
- (2) Contraction of plain muscle, *e.g.* of uterus. The production of contraction of plain muscle of the uterus is called the *oxytocic* action.
- (3) Expansion of the melanophores (pigment cells) of the frog's skin (Hogben and Winton), so that the skin looks darker in colour. (Especially by extracts of the *pars intermedia*.)
- (4) *Diuretic Effect.* In anæsthetised animals, a brief diuresis follows the injection.

(5) *Anti-diuretic Effect.* The posterior lobe has been removed in dogs without permanent ill effects. Immediately after removal, there may be a temporary increase in the urine, with diminution of chlorides. Puncture of the third ventricle has been found, in a number of cases, to be followed by a condition of diabetes insipidus, *i.e.* the excretion of large quantities of very dilute urine. Whether the effects of puncture of the third ventricle are to be ascribed to some defect in the absorption or production of a hormone in the posterior lobe, or whether, conversely, the effects of removal of the pituitary body are due to attendant damage to the hypothalamic region, is still debatable. But it is true that the condition of diabetes insipidus, however brought about, may be relieved temporarily by the subcutaneous injection of a watery extract of the posterior lobe ('*pituitrin*'). If injected into a normal man who has received a large draught of water, *pituitrin* delays the excretion of the water by the kidneys so that it accumulates for a time in the tissues and may even cause an actual dilution of the blood.

(6) *Galactagogue Effect.* Administration of pituitary extract to a lactating animal leads to sudden expulsion of milk, due to contraction of the plain muscle in the walls of the milk sinuses.

(7) *Effect on carbohydrate metabolism (glycosuria).*

The best known actions of this substance are its *pressor* effect, from constriction of the blood vessels, and its '*oxytocic*' action on the uterine muscle. For both these purposes *pituitrin*, in subcutaneous injection, is employed clinically.

According to Krogh, a certain content of *pituitrin* in the circulating blood is essential for the maintenance of the normal tone of the capillaries.

It has long been disputed whether these actions are to be attributed to a single active principle, or whether more than one such hormone is concerned, as was claimed by Dudley. Recent researches by Kamm and others have settled the discussion in favour of the latter, and the separated *oxytocic* and *pressor* principles can now be obtained on the market. The *antidiuretic* principle is associated with the *pressor* constituent.

OTHER ENDOCRINE ORGANS

The internal secretions of the *pancreas* and of the *gonads* are dealt with elsewhere (Chapters XXX and XLIV).

The *Thymus* forms two large masses in the anterior mediastinum, which in man grow up to the second year of life and then rapidly diminish, so that only traces are to be found at puberty. It contains a large amount of lymphatic tissue and is therefore often associated with the lymphatic glands as the seat of formation of lymph corpuscles. The epithelial structures called Hassall's corpuscles, found in the medullary part of its lobules, have not had any function assigned to them. In certain cases of arrested development or of general weakness in young people, the thymus has been found to be persistent. The effect of extracts made from the thymus do not differ from those of extracts made from any other cellular organ. It is very doubtful whether the thymus should be counted as one of the endocrine organs.

It has been stated that when tadpoles are fed on thymus gland their metamorphosis is retarded, so that enormous tadpoles are obtained. Thyroid feeding has the reverse effect, hastening metamorphosis, so that minute frogs are produced.

The *Pineal Gland* has so far not been proved to have any function in metabolism. It is interesting as a vestigial remnant of a primitive dorsal eye. It has been claimed that removal of the pineal body in young animals, or destructive pineal tumours in young boys, results in obesity, premature sexual development and early maturity. Feeding of tadpoles with pineal substance rapidly produces pallor, due to contraction of the melanophores in the skin.

The *Carotid* and *Coccygeal Glands* have often been grouped with the collections of chromaffine cells already described as associated with the sympathetic system. They consist of a small collection of columns or masses of cells bound together by connective tissue with a rich supply of blood capillaries.

THE MUTUAL INTERACTION OF HORMONES

Every ductless gland, like every other organ of the body, is subject to the action of other ductless glands. The production of any one hormone is therefore never an isolated event, since the hormone may influence other ductless glands or tissues producing hormones, so that a whole chain of processes is started, the extent of which it is difficult to define. We have seen that there is some connection, at present but little understood, between the pituitary and the thyroid. But there are other examples, more complex than this, of interrelations between different ductless glands. Thus, if we can speak of a 'sugar function' of the body, including in this the whole metabolism of carbohydrates, we know that the presence of insulin is necessary if it is to be carried out normally. Absence of insulin from the blood causes hyperglycæmia—excess hypoglycæmia. Injection of pituitrin prevents the hypoglycæmia due to injection of insulin. Adrenaline causes hyperglycæmia, and diminishes the effect of insulin, and a secretion of adrenaline normally occurs whenever the blood sugar falls to a low level, and thus tends to restore it to normal. Excessive secretion of the thyroid hormone not only apparently stimulates adrenaline production and augments the action of the sympathetic nervous system, or of adrenaline, but diminishes the sugar tolerance of the animal, and may be attended with actual glycosuria. On the other hand, atrophy or excision of the thyroid increases the sugar tolerance of the body, and the same result is found in the infantilism due to atrophy or extirpation of the anterior lobe of the pituitary body. There is apparently

a close co-operation between the suprarenals and the thyroid in response to fever, cold, and other disturbances of the heat regulation. Hypertrophy of the cortex of the suprarenal causes precocious development of the generative organs, and thereby a premature development of secondary sexual characters. Absence of the thyroid prevents sexual development, and therewith the growth of the body as a whole.

There is evidently here a whole chapter of physiology to be opened up, which cannot fail to be of importance for the understanding of many processes of disease. At present, though theories abound, our knowledge is limited to fragmentary facts, such as these just enumerated, and we must await further research before we can form any connected idea of the manner in which the different functions of the body are integrated by the interplay of the endocrine organs.

BOOK V
REPRODUCTION

CHAPTER XLIV

THE REPRODUCTIVE PROCESS

THE ESSENTIAL FEATURES OF THE SEXUAL PROCESS

THE two fundamental characteristics of protoplasm, which distinguish it above all others from unorganised matter, are *growth* and *activity*. Growth occurs at the expense of surrounding non-living material, while activity is a reaction to changes in the environment. In the process of growth of a minute spherical mass of protoplasm, its bulk and mass increase as the cube, while the surface increases only as the square of the radius. Thus the proportion of surface to mass diminishes with increased size of the protoplasmic unit and, since activity is a function of the surface, the larger the unit the smaller, relatively, must be its activity. It follows that there must be a limiting size to the living cell, and it is on this account that hardly any unicellular animal or plant exceeds a fraction of a millimetre in diameter. If an organism is to attain any larger size, this can only be by a multiplication of units, each presenting the same relative amount of surface as a complete unicellular organism, though that surface may be exposed to an internal and not to an external medium. Another factor, limiting the size of the unicellular organism or of the unit of the multicellular organism, is the necessity for maintaining a certain proportion between the size of the nucleus and that of the cytoplasm composing the body of the cell. Hence, when for any reason it is advantageous that a cell should attain a large size, such a cell is almost always found to contain many nuclei. All the 'giant cells' found in the body of man under normal or pathological conditions are also multinuclear.

REPRODUCTION IN THE PROTOZOA. Thus the continuous display of the functions of assimilation and dissimilation, of growth and activity, is possible only so long as cell division keeps pace with growth. In unicellular organisms under favourable conditions, this growth and multiplication occur with prodigious rapidity. It has been computed that a paramœcium, freely supplied with food material, would, by growth and division, in the course of a year represent a mass of protoplasm the size of the earth, assuming, of course, that no accidents or destructive agencies intervened to destroy the paramœcia which were being formed. This computation, which may seem a fanciful one, is useful as indicating the enormous number of individuals brought under the action of natural selection, which very few survive. In unicellular organisms, such as paramœcium or amœba, death cannot be regarded as a natural process. They may be eaten by higher organisms or serve as food to vegetable parasites, but so long as conditions are favourable and food supply sufficient, they will continue to grow and reproduce themselves eternally. In the course of its existence each individual may be brought under many varieties of conditions; some of these may be so harmful that the individual is destroyed and its race comes to an end. Other individuals under circumstances of less severity, may undergo spontaneous modifications in their structure which serve to neutralise the effect of the injurious environment. Such modification in structure, morphological or molecular, might be transmitted to the next generation, so that, with slowly varying external conditions there is a possibility of a corresponding slow variation in type, which may finally attain a form altogether different from that with which it set out. A new species may, in this way, be formed by gradual alteration of environment. It is therefore not difficult to understand, in the case of such organisms, either the maintenance of type by heredity under constant conditions, or the change of type with gradually varying conditions.

Reproduction by continuous growth and division is not, however, the only means, even in the unicellular animals, by which new generations may be produced. If protozoa, such as paramœcia, be kept for a long time in nutrient solutions, their vitality and their rapidity of reproduction falls off. Under these conditions, a new phenomenon makes its

appearance, viz. 'conjugation,' which is the analogue of the sexual reproduction of the higher animals. Infusoria contain two kinds of nuclei, a large and a small, known as the *macro-nucleus* and the *micro-nucleus* respectively. During conjugation, the macro-nucleus breaks up and disappears in the two cells, which become closely applied together, while in each of them the micro-nucleus divides twice to form four spindle-shaped bodies. Three of these degenerate (like the polar bodies of the ovum), while the fourth divides into two germ-nuclei. This is followed by an exchange of germ-nuclei, one from A passing into B, while one of those from B passes into A. The two cells then separate, a single micro-nucleus being formed in each by the amalgamation of the two. This micro-nucleus then divides three times, so that eight nuclei are formed, while the cell itself divides into four, two nuclei passing into each of the daughter cells. Of these, one enlarges to form the macro-nucleus, while the other remains as the micro-nucleus. After conjugation has occurred, the colony of infusoria takes on, so to speak, a new lease of life, and there is a rapid production of new generations by simple division of the cells, in which both macro-nucleus and micro-nucleus take part. It is very difficult to understand the advantage of this interchange of nuclear material either to the individual or to the race. It should be noted that the half of the nucleus lost by each conjugating organism is qualitatively different from that which it retains and probably from that which it receives. It has been suggested that, as soon as each individual concerned in the process receives the nuclear material from organisms which may have been exposed to slightly different circumstances, corresponding changes will be introduced into the tendencies to growth of the product of the union. Some of these tendencies may be more advantageous than before, while others may be the reverse. Increased possibility of variation is however introduced by this admixture of nuclear material, and this may be the advantage of the process to the race.

REPRODUCTION IN THE METAZOA

The numberless cells forming the bodies of the higher animals are all produced by a series of divisions from a single cell, the fertilised ovum. This cell is the result of a process of conjugation between two cells derived from different individuals. With the multiplication of cells forming a single organism there is, of course, an increased size of the organism. It is doubtful whether this would of itself be of any advantage, were it not that the multiplication of cells goes hand in hand with differentiation, which implies higher functional capacity. Specialisation of function involves changes of type in the cells resulting from the division of the primitive undifferentiated ovum. In most cases this change of type is permanent. An epithelial cell, such as that forming the epidermis or the liver, when it divides, produces another cell of the same kind. Differentiation necessarily brings with it a limitation of the powers of reproduction. Any one of the descendants of an unicellular organism is in all respects equivalent to its ancestor, and can reproduce the same type of individual. The specialised liver or muscle cell can produce only a cell of the same type, one, that is to say, incapable of independent existence or of forming the divergent series of types necessary for the production of an individual. Differentiation of function therefore involves the setting aside of special cells, *germ cells*, which retain their primitive character and are capable of indefinite division to form new generations each able to develop into a complete individual. These germ cells can often be recognised from the very earliest divisions of the fertilised ovum, which lead to the production of the mature individual. Thus, in *Ascaris*, the progenitor of the germ cells differs from the somatic cells both by the greater size of its nucleus and in its mode of division (Fig. 525). In the cells destined to produce the somatic cells, a portion of the chromatin is cast out into the cytoplasm, where it degenerates, so that only in the germ cells is the sum total of the chromatin retained. Thus, in the two-celled stage, in one cell all the chromatin is preserved, while in the other cell the thickened ends of the chromosomes are cast off into the cytoplasm and degenerate, only the thinner central portions

being preserved. When these divide again, the same process is repeated in only one of the daughter cells derived from a germ cell, and this recurs during five or six divisions, after which the chromatin elimination ceases and the two primordial germ cells thenceforward give rise only to other germ cells in which the entire chromatin is preserved. Thus "the original nuclear constitution of the fertilised egg is transmitted, as if by a law of primogeniture, only to one daughter cell, and by this again to one, and so on, while in other daughter cells the chromatin in part degenerates, in part

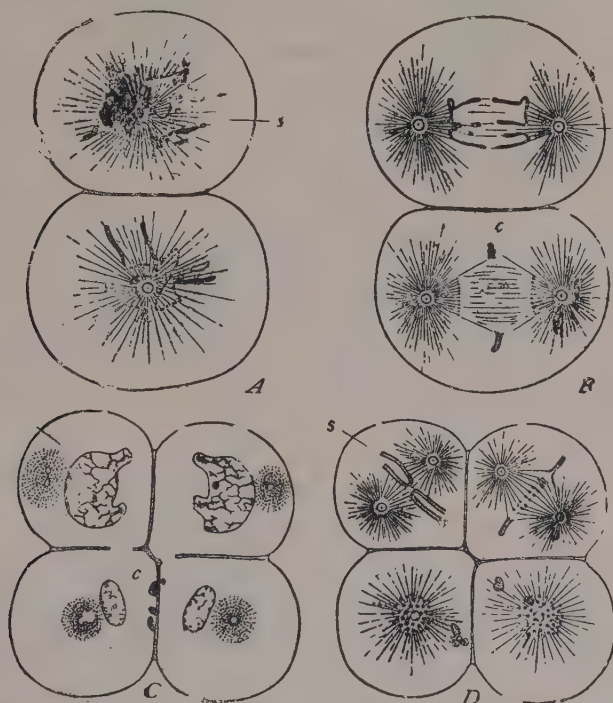


FIG. 525. Origin of the Primordial Germ Cells and Casting out of Chromatin in the Somatic Cells of *Ascaris*. (WILSON and BOVERI.)

- A. Two-cell stage dividing.
- s. Stem cell, from which arise the germ cells.
- B. The same from the side, later in the second cleavage, showing the two types of mitosis and the casting

- out of chromatin (c) in the somatic cell.
- C. Resulting four-cell stage; the eliminated chromatin at c.
- D. The third cleavage, repeating the foregoing process in the two upper cells.

is transformed, so that all of the descendants of these side-branches receive small reduced nuclei" (Boveri, quoted by Wilson).

The immortality, which was the property of all the unicellular ancestors of the metazoa, has, in the latter, descended only to the germ cells. All the other cells of the body, which form the nervous and muscular tissues, glands, skin, etc., are mortal. They pass through a certain number of divisions; but although this number is large, it is limited, and on the number of divisions which are possible depends the normal duration of life of the organism to which the cells belong. We may thus regard the egg cell as dividing into two parts. From one part will be formed by differentiation all the complex somatic mechanisms of the adult animal; the other part will divide, but will remain in an undifferentiated form, until its descendants

can conjugate with germ cells from other individuals to form fertilised egg cells, destined to undergo the same series of changes.

The metazoan individual thus consists of a mortal host holding within itself the immortal sexual cells or gonads. Gaskell has pointed out that the development of the fertilised ovum involves two parallel processes—the elaboration, on the one hand, of the elements forming the host; on the other, of those derived from the independent germ cells. From the very beginning, the somatic part of the organism, the host, is a reacting individual, in which the nervous system acts as the integrator of all the activities of the body and as the middleman between the internal and external epithelial surfaces and the muscular system. Thus, the evolution of the animal kingdom means essentially the evolution of the host, and must therefore be closely connected with the evolution of the central nervous system, the ruling element in the neuro-muscular syncytium.

All the complex mechanisms which are concerned in maintaining the life of the individual have apparently been developed in order to give the potentially immortal germ cells a better chance of survival in the struggle for existence. From the broad biological standpoint, as Foster points out, all the toil and turmoil of human existence may be regarded simply as the by-play of an ovum-bearing organism. From the same standpoint, one must acknowledge that the mortality of the individual must be an advantage to the race. Throughout the living world the welfare of the individual is subordinated to that of the species. With each new generation there are possibilities of variation and of the production of individuals better or worse fitted for the maintenance of the race than those of the previous generation. Immortality of the individual would handicap the survival of the younger generations, and result in retardation of progress.

THE FORMATION OF GERM CELLS

In multicellular organisms, the cells which conjugate to form a new cell, capable of developing into an individual, are of two kinds. One, which has generally a certain amount of reserve material stored up in its cytoplasm, is the female element and is called the *ovum*. The other cell, which consists of little more than nuclear material, is the male element and is called the *spermatozoon*. Both kinds of cells are derived from the germinal epithelium which, as we have seen, can sometimes be traced directly back to the first divisions of the fertilised egg. The use of the reserve material in the ovum is to serve as food for the developing individual. The ripe ovum and spermatozoon cannot be regarded as complete cells, but rather as half-cells. Before their union or conjugation both male and female germ cells undergo certain important changes which further differentiate them from the somatic cells of the individual. The essential differences between a ripe germ cell and a somatic cell can be best seen by a study of the nuclear changes which precede their formation.

MITOTIC DIVISION. In division, the nuclei of all somatic cells, whether of plants or animals, undergo a series of changes which, in their broad outlines, are similar throughout both animal and vegetable kingdoms (Fig. 526), and result in the production of qualitatively identical daughter nuclei.

The nucleus of the resting cell in its vegetative condition is generally separated from the cytoplasm by a nuclear membrane, and contains irregular masses of chromatin. In the cytoplasm of most animal cells may be seen a small particle known as the centrosome. When division is about to take place, the clumps of chromatin arrange themselves into a filament which forms a continuous skein, the 'spireme stage.' This then breaks up into a number of segments, often V-shaped, the chromatin filaments or *chromosomes*. Each of the filaments, in large nuclei, may often be seen to be composed of rows of granules. While this change has been occurring, the nuclear membrane in

most cases disappears, and the centrosome outside the nucleus divides into two parts which travel to opposite ends of the nucleus. Round each centrosome, the cytoplasm is modified and presents a radiate appearance, the *aster*, while joining the two centrosomes is a spindle of fine fibres, the *achromatic spindle*. The V-shaped segments of chromatin arrange themselves in a circle at the equator of the spindle midway between the two centrosomes. Each of the loops then splits longitudinally, and each half travels towards

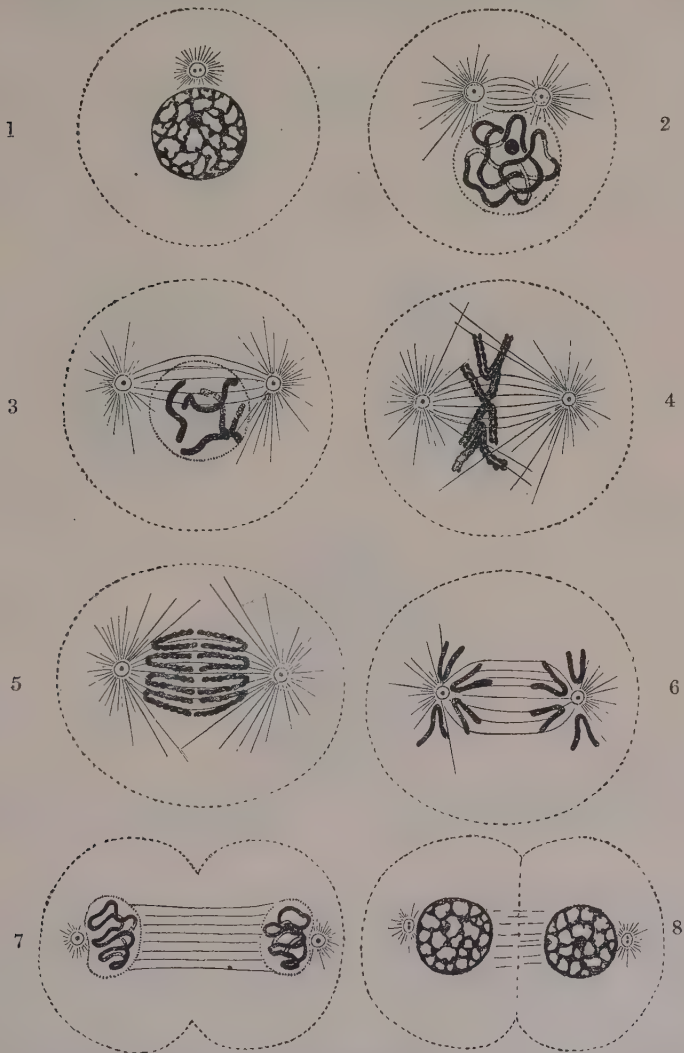


FIG. 526. Diagram showing the Changes which occur in the Centrosomes and Nucleus of a Cell in the Process of mitotic Division. (SCHAFER.)
The nucleus is supposed to have four chromosomes.

one or other of the centrosomes, thus forming two daughter nuclei. The half-loops then join to form a skein, and may return to the condition of a resting nucleus. The entire process, as seen in tissue cultures, takes about two or three hours, though probably about twelve hours elapse between the commencement of division in a cell and the beginning of renewed division in the daughter cells. These different phases in division are presented by all somatic cells, and have received the following names :

(1) *Prophase* (the formation of the spireme and of the achromatic spindle, and the breaking up of the spireme into chromatin loops or chromosomes). This phase occupies from ten minutes to an hour, probably as a rule about thirty minutes.

(2) *Metaphase* (the splitting of the chromosomes). This takes from two to twelve minutes.

(3) *Anaphase* (the travelling of each half-chromosome to the extremity of the spindle), which occupies about three to five minutes.

(4) *Telophase* (the retrogressive changes, leading to the conversion of the chromatin filaments into an ordinary resting nucleus, which are accompanied or preceded by a division of the cytoplasm across the equatorial part of the spindle). The latter part of the process takes about three to twelve minutes, but the retrogressive changes take from thirty minutes to two hours.

When the spireme has broken up into separate chromatin loops, it is possible to count them, and it is found that the number present in any cell (diploid number), is constant for the species. Thus, every human somatic cell has forty-eight chromosomes in its nucleus. Identical numbers are found in types so far apart as the ox, the guinea-pig, and the onion. In the mouse, the salamander, and the lily the number is twenty-four. Other types, such as the crustacean *Artemia*, are said to have as many as 168 chromosomes, the much-investigated fruit-fly, *Drosophila melanogaster*, has eight, while in *Ascaris*



FIG. 527. Three Stages of Heterotype Mitosis in Spermatocyte of Triton. (MOORE.)

a. Germinal condition of chromosomes.
b. Gemini arranged in quadrate loops or tetrads.

c. Separation of tetrads into the duplex chromosomes of the daughter nuclei.

the cells contain only two or four chromosomes. There is usually an even number of chromosomes, and these are arranged in homologous pairs, the chromosomes of each pair being similar in size and shape (v. Fig. 532). On division, each chromosome gives rise to daughter-chromosomes of exactly similar shape and size. The somatic type of cell division, called *mitosis* or *karyokinesis*, seems to be adapted to ensuring an equal qualitative as well as quantitative distribution of the nuclear chromatin among the daughter cells resulting from the division of any cell. As we have seen in an earlier chapter, the nucleus, by its interaction with the cytoplasm, determines the processes of assimilation and growth of the whole cell. For the preservation of type in cell division it is therefore essential that the nuclei of the daughter cells shall be identical in all respects with the nucleus of the mother cell.

REDUCTION DIVISION. Sexual reproduction involves the conjugation of two cells, with union of their nuclei. If each of these nuclei consisted of the normal number of chromosomes, the fertilised egg cell would contain double the number characteristic of the species, and since these chromosomes would divide by splitting, the number of chromosomes in each cell would be doubled with each generation. This doubling is obviated by the fact that, in the formation of the germ cells, the ovum and spermatozoon nuclei undergo a

special type of division, which leads to the reduction of the chromosomes in the sexually mature cell to one-half of the number characteristic of the species. This mode of cell division is often called 'division by reduction,' or 'hetero-type' mitosis, or 'meiosis' (Figs. 527 and 528).

We may take as an example the development of spermatozoa. The mother cells of the spermatozoa, the *primary spermatocytes*, divide twice, giving rise to four daughter cells, the *spermatids*, each of which develops into a functional spermatozoon. In the nuclear changes preparatory to the first division, the chromosomes become grouped together in pairs. At the first, or reduction division, the members of each pair, instead of being split longitudinally, are separated, so that each of the resulting

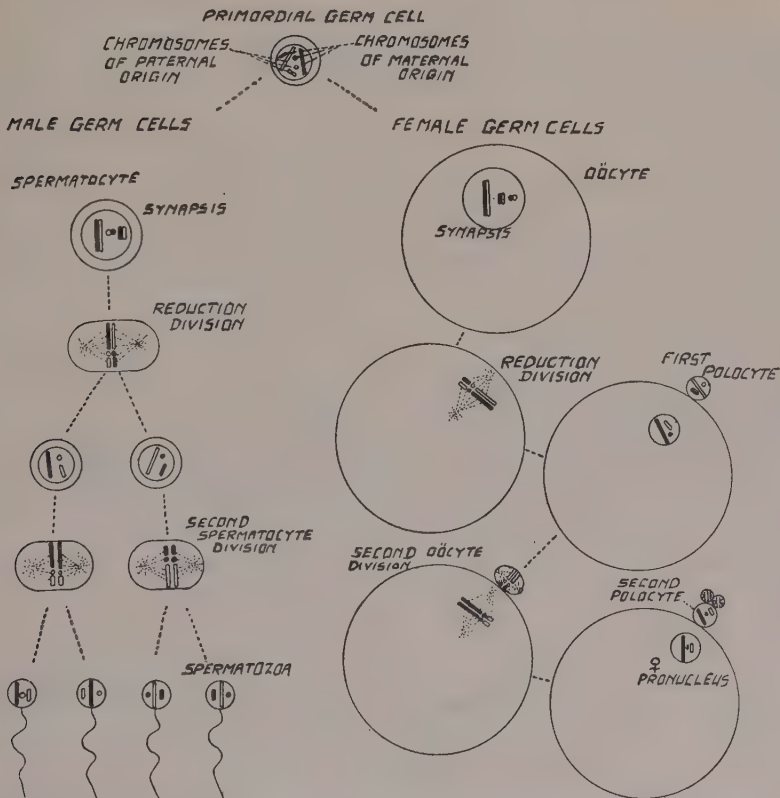


FIG. 528. Diagram to illustrate Formation of Germ Cells with Haploid Number of Chromosomes. (LUDFORD.)

cells receives one member of each pair and hence contains only half the somatic number of chromosomes. At the second division, these are split in the usual way. The distribution of the paired chromosomes to the daughter cells at reduction provides the possibility of qualitative differences between them, since the half which goes to each daughter cell represents one of the two chromosomes which form a pair in cells of the somatic type. If we indicate the four normal chromosomes as *a, b, c, d*, of which *a* and *b* form one pair and *c* and *d* form the other, in ordinary somatic division each daughter cell will also contain chromosomes which may be represented as *a1, b1, c1, d1*, and *a2, b2, c2, d2*. But on reduction one daughter cell receives *a* and *c*, while the other daughter cell receives *b* and *d* in the usual way. Exactly similar changes take place when there are larger numbers of chromosomes, one member of each pair of somatic chromosomes finding its way into the ripe spermatozoon.

The mitochondria and Golgi apparatus can be traced throughout all the stages of spermatogenesis, and are approximately shared out in the cell divisions. In the forma-

tion of the spermatozoa from the spermatids, well-marked changes occur in the cytoplasmic inclusions. The tail of the spermatozoon arises in association with one of the centrioles. In the mature spermatozoon the head is derived from the nucleus of the spermatid; the acrosome, which forms a cup of variable shape according to species, is formed in association with the Golgi apparatus, in a manner somewhat similar to that of

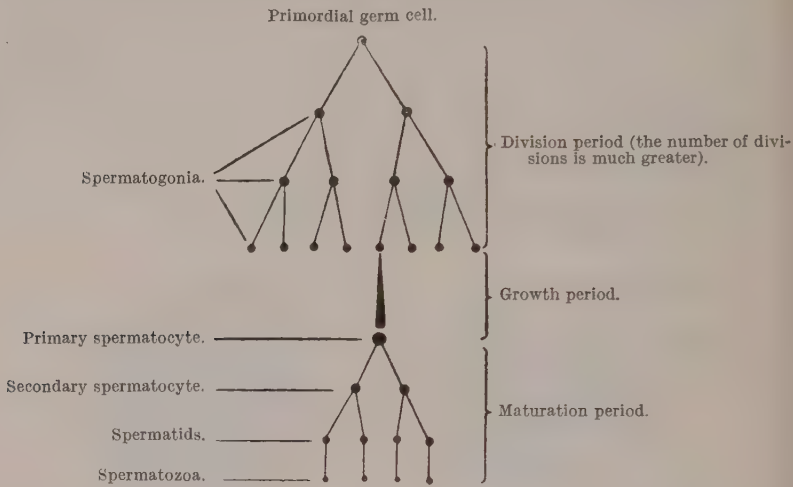


FIG. 528.

the formation of granules in gland cells. The middle piece is of cytoplasmic origin and composed largely of mitochondria in spiral formation.

In the ovum, during maturation, analogous changes takes place. Two successive cell divisions occur as in the formation of spermatozoa, but the daughter cells are of very unequal size. In the first division, the heterotypical division, the chromosomes pairs separate as in the spermatocytes, so that each of the daughter cells contains one half the

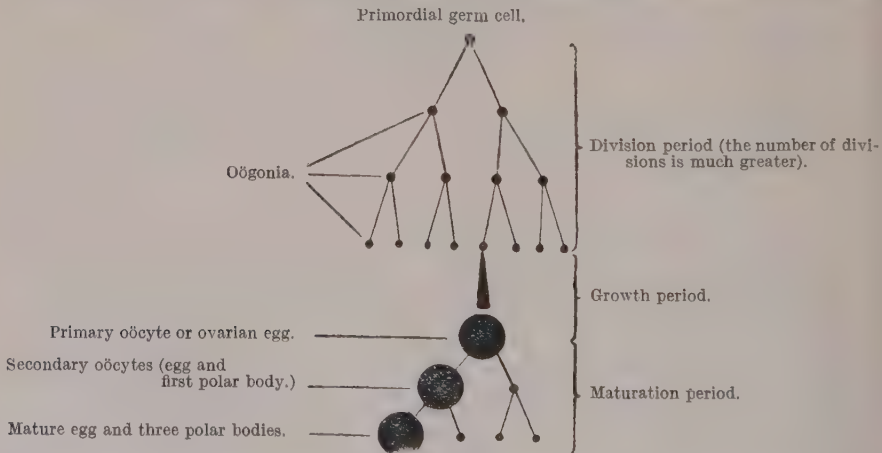


FIG. 529.

somatic number of chromosomes, and, as in the male, each of them represents one of a pair of similar chromosomes present in the somatic cells. The larger of the two resulting cells, which retains most of the cytoplasm, is still called the ovum, while the smaller one is spoken of as the 'first polar body' or 'first polocyte.' The ovum now divides again and throws off a second polar body, the division being of the usual homotypical variety. The first polar body also divides, so that, from the original ovum, four cells are produced, one of which retains the greater part of the cytoplasm, while the others are extruded, and degenerate (Figs. 528 and 529). The only difference, therefore, between the formation of

ovum and spermatozoon is that in the former case three of the cells formed by the division of the primitive ovum are abortive, whereas in the spermatozoon all four daughter cells produced from the spermatocyte remain functional. The number of chromosomes characteristic of somatic cells in a given species is called the *diploid* number, and that found in the ripe gametes the *haploid* number. Since the nuclei of the mature ovum and spermatozoon contain only half the somatic number of chromosomes, they are generally spoken of as *pro-nuclei*.

In oögenesis, the mitochondria increase in numbers and are evenly distributed in the cytoplasm of the ripe cell. The Golgi apparatus similarly becomes spread out, and in some cases yolk is formed in association with it; in the mammal, however, it merely spreads out, usually near the periphery.

FERTILISATION

The essential features of fertilisation, *i.e.* the union of the sexual cells, are best studied in some of the lower invertebrates, such as ascaris or echinoderms. In the latter, fertilisation takes place in the sea-water, into which both ova and spermatozoa are extruded. The ovum of the echinoderm consists of a naked mass of protoplasm. Of the countless hordes of spermatozoa which may be in the neighbourhood of a given ovum, only one, as a rule, enters. As soon as the spermatozoon has entered the ovum, a tough membrane is rapidly formed round the latter, so preventing the entrance of any further spermatozoa. The head of the spermatozoon enters the egg, while the tail atrophies and disappears. The head of the spermatozoon enlarges and assumes the character of a nucleus, the dense mass of chromatin breaking up first into a thread and then into the characteristic haploid number of chromosomes (Fig. 530). The egg now contains two nuclei or pro-nuclei, exactly similar in appearance, one derived from the male and the other belonging to the egg itself. The two nuclei approach one another and join. In many cases, there is an apparent fusion of the substance of the two nuclei. In others, the chromatin filaments of male and female simply lie side by side, forming a complete nucleus with the diploid number of chromosomes. The fate of the remainder of the spermatozoon is uncertain: it has been suggested that the acrosome plays some essential physico-chemical part in fertilisation, but there are no indications of what this may be. In some rare cases, the mitochondria of the spermatozoon have been seen to enter the cytoplasm of the ovum and mingle with those already there. Fertilisation is rapidly followed by an enormous increase in metabolism, *e.g.* in the oxygen consumption, and by cell division. Each of the chromosomes splits longitudinally, half going to each of the daughter cells, and this process is repeated throughout the succeeding divisions which result in the formation of the new individual. Thus, every cell of the body contains a nucleus of which exactly one half is paternal and the other maternal in origin.

The strong impetus to cell division given by the process of fertilisation has naturally aroused much curiosity as to its intimate character. It might be thought that, for cell division to take place, a normal number of chromosomes is essential. As against this explanation may be adduced the fact that, in many animals, *parthenogenesis* occurs. The female pro-nucleus may, under certain conditions of environment or nutrition, start dividing and give rise to an embryo, each cell of which contains only the haploid number of chromosomes. In other cases of parthenogenesis, only one polar body is extruded, or the second polar body joins again with the female pro-nucleus. In these cases, the ovum contains a nucleus, with a normal number of chromosomes, which divides and produces an individual resembling that resulting from the union of ovum and spermatozoon. It has been suggested that the impetus to division is given by the entry of the spermat-

zoon itself. In the series of divisions which precede the formation of the female pro-nucleus, the centrosome of the ovum generally disappears, whereas in the formation of the spermatozoon, the centrosome persists and forms the middle part of the spermatozoon. In many cases, the centrosomes divide

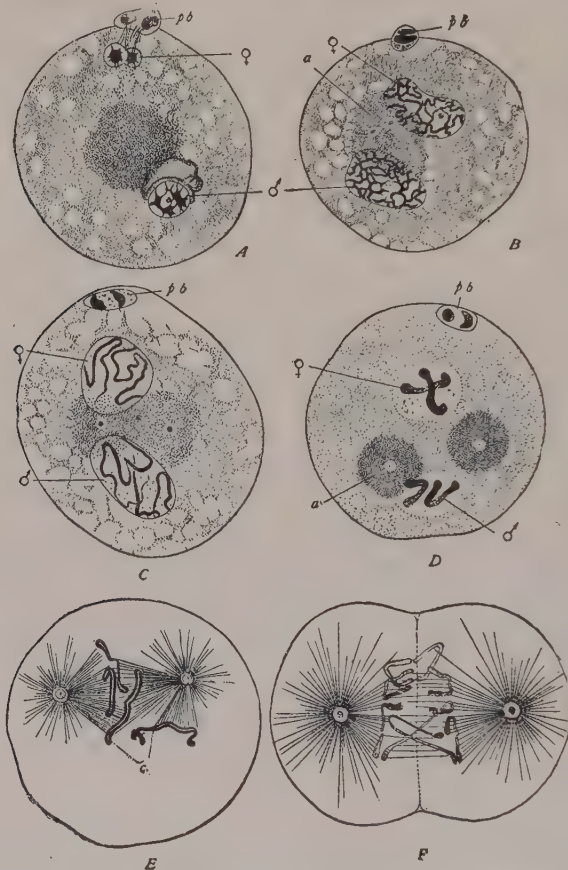


FIG. 530. Fertilisation and First Division of Ovum of *Ascaris Megalocephala*.
(Slightly modified from BOVERI and WILSON.)

A. Second polar globule just formed; the head of the spermatozoon is becoming changed into a reticular nucleus (σ), which, however, shows distinctly two centrosomes; just above it, its archoplasm is shown; the egg nucleus (φ) also shows two chromosomes. B. Both pro-nuclei are now reticular and enlarged; a double centrosome (a) is visible in the archoplasm which lies between them. C. The chromatin in each nucleus is now converted into two filamentous chromosomes; the centrosomes are separating from one another. D. The chromosomes are more distinct and shortened; the nuclear membranes have disappeared; the attraction spheres are distinct. E. Mingling and splitting of the four chromosomes (c); the achromatic spindle is fully formed. F. Separation (towards the poles of the spindle) of the halves of the split chromosomes, and commencing division of the cytoplasm. Each of the daughter cells now has four chromosomes; two of these have been derived from the ovum nucleus, two from the spermatozoon nucleus.

in the spermatozoon itself, so that this contains two centrosomes when it enters the egg. These two centrosomes then become the centres of attraction spheres. They diverge, and between them is formed an achromatic spindle, along the equator of which the chromatin filaments of male and female pro-nuclei arrange themselves. It is doubtful, however, how far the centrosome can be regarded as a permanent cell structure.

In echinoderm eggs, various modes of treatment will lead to the appearance of attraction spheres in the cytoplasm, and even to division of the non-fertilised egg. Loeb has suggested that the action of the spermatozoon is essentially due to a destructive action on the cortical layer of the ovum, which may be chemical in nature. By the addition of mild cytolytic agents to the medium in which the eggs are contained, Loeb has succeeded in imitating exactly the changes which normally need the entrance of a spermatozoon for their occurrence. On immersing the eggs in a weak solution of formic or lactic acid, a membrane is formed. The eggs are then taken from the acid, placed in concentrated sea-water for a short time, and then removed to ordinary sea-water. Division rapidly occurs, with the production of the normal larva. This artificial 'fertilisation' is called *artificial parthenogenesis*. He suggests that the spermatozoon brings with it enzymes or other chemical substances, which excite the egg nucleus and cytoplasm in the same way as the chemical measures adopted for this artificial induction of segmentation.

Mechanical damage to the outer part of the ovum may also lead to parthenogenetic development, as for instance of the unfertilised frog's egg when punctured with a needle.

DEVELOPMENT AND HEREDITY

From the fertilised egg, there is formed an individual partaking of the minutest characteristics of both its parents. An egg cell has much the same appearance, whether it belong to an echinoderm, a fish, or a woman. In the process of development, by a simple repetition of a series of cell divisions, this undifferentiated protoplasm is formed into the complex organs with the potentialities and habits which distinguish the type from which it has been derived. There must, therefore, be some difference between different eggs. We cannot wonder that the intimate nature of this process has been the subject of speculation from the very birth of science. Running through these speculations are two main ideas, which have been labelled the theories of 'evolution' and of 'epigenesis.' By the 'evolutionists' the egg was believed to contain an embryo fully formed in miniature, as the bud contains the flower or the chrysalis the butterfly. Development therefore, was only the unfolding of something already existing. If, however, this theory be pushed to its utmost and if the egg contain a complete embryo, this must itself contain eggs for the next generation, and so on *ad infinitum*, a conclusion which of course is absurd. According to the theory of epigenesis, the structure of the egg is wholly different from that of the adult, its development into the new individual consisting in the continual formation, one after the other, of new parts previously non-existent as such. There is no doubt that this view is fundamentally correct. The difficulty with which we have to contend is the understanding of the orderly sequence and correlation of the cell divisions and differentiations which result in an adult individual of the same type as the parents. The fact that, under approximately identical conditions, one mammalian ovum will give rise to a mouse and the other to a man, indicates that there must be some preformed differentiation in the nuclear structures, *i.e.* chromosomes, of the ovum itself. We have already seen that in some types the germ cells are separated off from the rest of the embryo at a fairly early stage. If, in the two-celled stage of the frog's egg, one cell be destroyed by means of a hot wire, the other cell develops to form half an embryo, thus suggesting that each cell of the two-celled embryo could give rise only to the corresponding half of the body. This limitation of development, however, occurs only if the

intact cell be left in connection with the cell that has been injured. If, in echinoderm larvæ, the cells be entirely separated, even as late as the eight-celled stage of division, each cell will give rise to a whole embryo, differing from a normal embryo only in respect of size. In man too, 'identical twins' result similarly, from separation of the two cells formed by the first division of the fertilised ovum. This suggests that the number of divisions that each cell can undergo is predetermined in the egg cell itself, but shows also that the cells into which the egg divides are, at first at any rate, equipotential. We must assume, therefore, that the reason why one cell under ordinary circumstances forms only one half of the embryo is that its development is regulated and determined by the presence of the other cell in connection with it and forming the other half of the embryo. That is to say, the development of the egg involves the adaptation to environment of a protoplasm of certain properties and powers of reaction. The final product of development depends (1) on the nature of the protoplasm (including the nucleus) of which the egg is composed, and (2) on the environmental conditions to which the egg is subjected during the rapid growth and multiplication attending its development. We could therefore speak of a morphology of inheritance, but the morphology would be ultra-microscopic and have relation to the molecular structure of the protoplasm of which the egg was composed.

In the transmission of the potentialities of development, from parent to fertilised egg, we must regard the nucleus as the essential structure. In ordinary development the spermatozoon furnishes only half a nucleus and a centrosome, the ovum supplying the whole of the cytoplasm. In division of the egg, the only part of the cell which can divide so that each daughter cell shall include an equal part of both parental germs is the nucleus. The constant number of the chromosomes in each species, and their accurate division on mitosis, suggest that the hereditary transmission of the potentialities of the cell is bound up with the chromosomes. It has been suggested that every inheritable character is located in a chromosome, or part of a chromosome. If this be the case, one might regard the differentiation into various tissues, which occurs in the process of development, as occasioned by an actual loss or degeneration of the constituent parts of one or more of the chromosomes present in the pluripotential fertilised egg-cell. There is no doubt that many tissues do become thus differentiated at a fairly early period in development, having undergone in the process an absolute modification of their potentialities, which must be at any rate shared by the chromosomes of their constituent cells. The extent to which this limitation of powers of development occurs varies widely in different animals. In the higher animals, such as man, epithelium will reproduce epithelium and liver cells will reproduce liver cells, while nerve cells once definitely characterised are absolutely incapable of multiplication. On the other hand, in crustacea, a whole limb may be torn off and be regenerated from the tissues of the stump. Destruction of the optic lens in the salamander is followed by its regeneration from the anterior part of the optic cup, a tissue which had no part in its primary formation. Worms will form a new head after decapitation. In these animals, therefore, the cells in many parts of the body possess the power of directed growth, if need arise in case of injury, and are able to form tissues of many different kinds.

We have mentioned the small size of the larva formed from isolated cells of the segmenting egg as a proof that the number of cell divisions of the somatic part of the developing animal is predetermined and limited. This conclusion must not be taken too absolutely. Many of the tissues, even of

the highest animals, possess the power of almost unlimited regeneration by cell multiplication as a response to injury. Under normal conditions, the growth of such tissues is limited, not by absence of power to divide, but as a result of a mutual interaction between them and the surrounding cells. We might almost speak of a struggle for existence between the various tissues of the body, which, in the healthy organism, results in a balance of multiplicative powers. If this balance is upset by any means, such as stimulation of certain cells by the presence of intracellular parasites, or their destruction by irritants or other abnormal conditions (*e.g.* exposure to X-rays), one tissue may enter into active growth at the expense of the surrounding tissues, and the result is a morbid growth such as cancer. It is possible that in the latter case a new factor comes into play. All tissues of the body, as we have seen, begin to die from the time that they are born. They have a certain span of life, a certain limitation to their generations, which results in the phenomenon of senescence, such as occurs in a culture of protozoa. In protozoa this phenomenon is the signal for rejuvenation by conjugation. It is possible that, in cancer, something of the same nature occurs. It is, at any rate, significant that in a rapidly growing cancer, many of the dividing cells present the phenomenon of heterotype mitosis, a phenomenon which is otherwise found only in the sexual cells preparing for conjugation and for the production of a new individual. Given adequate conditions of nutrition, there seems to be no limit to the growth of cancer cells. In mice, a cancer may be transferred from one individual to another by inoculation, and this process may apparently go on indefinitely, so that finally, a mass of cancer cells may have been produced equal in volume to many thousands of mice, and persisting long after the mouse from which it was first taken would have died under natural conditions.

In sexual reproduction, the new individual partakes of characteristics of both its parents. It therefore resembles neither of its parents in all details. The conjugation of the two parent cells, from which it is derived, has been preceded by a throwing out of half the chromosomes from each parent cell. It is therefore natural to ascribe the variations, which occur among the members of one family, to a qualitative difference in the chromosomes which have been eliminated in the formation of their respective egg cells. Can we regard the chromosomes as representing separate qualities of the individual, or must we assume that all qualities are represented to a greater or less extent in every chromosome? In the case of many qualities, especially those which distinguish the species as apart from the individual variation or family characteristic, we must probably accept the latter idea as correct. In this case, the child can be regarded as representing an arithmetical mean of both its parents. In certain respects, however, a quality seems to be transmitted from parent to offspring, either completely or not at all. This is specially applicable to those characters which have been rapidly produced by artificial selection, characters which, if artificial selection be abandoned, rapidly disappear, with reversion to the type from which the special strain was ultimately produced. These characters are alternative or *allelomorphic*, *e.g.* tallness or shortness, blue-eyed or brown-eyed.

The way in which these characteristics are transmitted was first studied by Mendel and has been formulated as 'Mendel's laws.' The first law is that of the *segregation of characters*, and is illustrated by his first experiments, which were carried out on peas. On crossing a tall plant with a dwarf plant, seeds were obtained from which all the plants were tall. On recrossing the plants of this generation among one another, a third generation (F_2) was obtained, in which 25 per cent. of the plants were dwarfs and 75 per cent. were tall. Crossing the dwarf plants among themselves led to the production of dwarf

and cross, say, an individual who is BBaa with one who is bbAA, then the gametes of the first will be Ba and of the second bA, and the somatic cells resulting will be Bb Aa. These will produce gametes of types BA, Ba, bA and ba, in equal numbers, and when they are crossed, in accordance with the laws of chance, the offspring will be of the types **BBAA, BBaa, BbAA, BbAa, BBaa, Bbaa, bbAA, bbAa, and bbaa**, in the ratios 1 : 2 : 2 : 4 : 1 : 2 : 1 : 2 : 1 or, in every sixteen :

- 9 with both dominants A and B.
- 3 with one dominant (A) and one recessive (b).
- 3 with one dominant (B) and one recessive (a).
- 1 with both recessive characters (a and b).

The 9 : 3 : 3 : 1 is obtained obviously by the combination of two 3 : 1 ratios of dominant to recessive characters, *e.g.* in peas, A = tall, a = short, B = purple flowers,

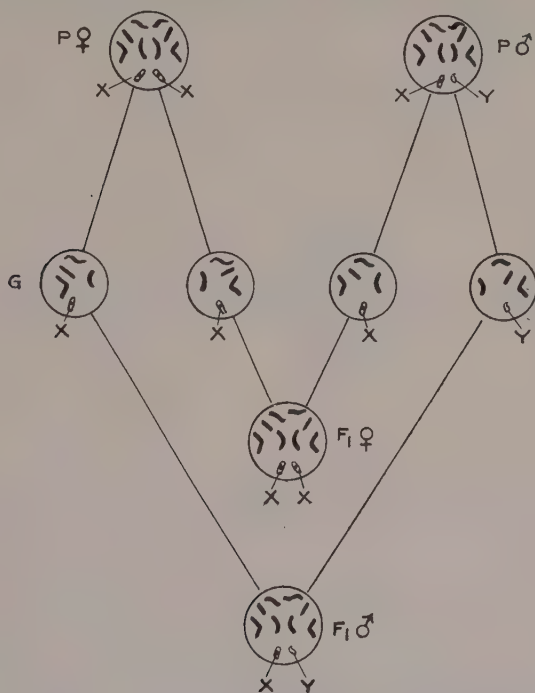


Fig. 531. Diagram to illustrate Principle of Sex-determination in an animal with 10 Somatic Chromosomes (5 pairs). P ♀, Female somatic cell. P ♂, Male somatic cell. G, The two ripe ova and two ripe spermatozoa (one X and one Y). F₁ ♀, Fertilised ovum which forms a female. F₁ ♂, Fertilised ovum which forms a male.

b = white flowers. If we cross a tall purple with a short white, the result will be all tall purples, but if these are self-pollinated we get :—

$$3 : 1 \left\{ \begin{array}{l} 12 \text{ Tall} = 9 \text{ purple} + 3 \text{ white,} \\ 4 \text{ Short} = 3 \text{ purple} + 1 \text{ white,} \end{array} \right.$$

3 : 1,

or, rearranged :—

$$3 : 1 \left\{ \begin{array}{l} 12 \text{ Purple} = 9 \text{ tall} + 3 \text{ short,} \\ 4 \text{ White} = 3 \text{ tall} + 1 \text{ short,} \end{array} \right.$$

3 : 1.

By similar independence, where three allelomorphic characters are considered, we get various combinations of dominant and recessive, in accordance with the laws of chance, with ratios 27 : 9 : 9 : 9 : 3 : 3 : 3 : 1. The possible variations in crossings where an indefinite number of characters are considered is thus limitless.

THE DETERMINATION OF SEX

In many animals it is known, and in all it is probable, that one of the somatic chromosome pairs are different in the two sexes, one sex having a certain pair of chromosomes, the 'sex chromosomes,' which are represented by only one, or by one complete and one vestigial chromosome in the other sex, and there is good reason to suppose that the initial determination of sex is connected with this difference.

When the reduction of the chromosomes takes place during gametogenesis and the individuals of each pair of chromosomes pass into different germ cells, one complete sex chromosome passes into each germ cell, in the sex that has two similar chromosomes, called XX (female in mammals); in the other sex where there is only one chromosome similar to these and the other one is either rudimentary (XY type) or lacking (XO), then one of the gametes will receive the X-chromosome, and the other one either no corresponding chromosome, or else the modified Y-chromosome. Thus the sex which is of XY or XO type (male in mammals) produces gametes of two kinds, while the gametes of the sex with the complete pair of sex chromosomes are of one type only. Thus when fertilisation takes place the original dimorphism of the zygotes is maintained. The chromosome mechanism at fertilisation is shown diagrammatically in Fig. 531.

The sex producing dimorphic gametes is therefore 'heterozygous' for sex, while the other is 'homozygous.' The study of the correlation between sex and chromosome constitution has been greatly facilitated by the study of sex-linked characters, such as

hæmophilia, their mode of inheritance lending strong support to the supposition that sex is initially dependent on chromosome constitution.

The sex carrying the extra chromosome varies in different groups of animals. In *Lepidoptera* and birds, for instance, the female is heterozygous and produces two kinds of ova, while the spermatozoa are of the same type, and in this case, therefore, the sex of the future embryo depends on the type of ovum fertilised. In *Diptera* and mammals (including man), on the other hand, the ova are all of the same type, but there are two kinds of spermatozoa. In the now well-known case of the fruit

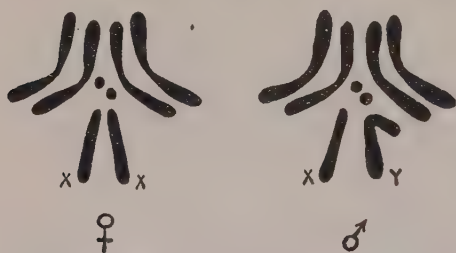


FIG. 532. Female and Male Groups of Chromosomes (Diploid) of *Drosophila melanogaster*. (After MORGAN, in Cowdry's *General Cytology*.)

fly, *Drosophila*, there are four pairs of chromosomes, comprising three pairs of ordinary chromosomes in both sexes, together with an XX pair in the female, and an X and Y in the male (Fig. 532). The spermatozoa are, therefore, of two types, having three ordinary chromosomes and an X, or three ordinary chromosomes and a Y. Ova fertilised by the former produce females, and those fertilised by the latter produce males. In the human subject the male again is heterozygous, the somatic number of chromosomes (according to Painter) being $46 + XX$ in the female and $46 + XY$ in the male. The spermatozoa, therefore, contain $23 + X$ or $23 + Y$, so that fertilisation of ova ($23 + X$) by the former results in females, and by the latter, in males. There is little doubt that, normally, the modelling of the embryo to the male or female pattern is primarily dependent upon its chromosome constitution, but there is equally little doubt that, in rare cases, other factors may lead to the chromosome constitution being over-ridden, causing the embryo to be partially or entirely diverted to the sex to which it was not predestined, and resulting in the production of intersexes or sex reversals.

LINKAGE.

Mendel's second law is not of universal application, owing to the existence of what is termed linkage. Experiment shows that certain factors are inseparable or only partly separable from certain others. Some factors are sex-linked, a good example being in *Drosophila*. When a white-eyed male is mated to a wild red-eyed female, all the first generations (F_1) are red-eyed. When these are inbred, the F_2 consist of three red eyes to one white, all the latter being males. When, as a fresh experiment, a red-eyed male is mated with a white-eyed female, then we get all the F_1 males white-eyed and all the F_1 females red-eyed. Consideration of these results indicates that the eye-colour factor is transmitted by the X-chromosome but not by the Y. Representing (WX) as the

chromosome with the linked gene red + sex, and (wX) as = white + sex, we have in the first case :—

$$P_1. \quad \begin{array}{cc} (wX)Y & \times & (WX)(WX) \\ (\text{male}) & & (\text{female}) \end{array}$$

$$F_1 = \underset{\text{(male)}}{(WX)Y} : \underset{\text{(female)}}{(WX)(wX)} \text{ (all red-eyed)}$$

$F_2 = (WX)(WX) : (WX)(wX)$, Females all red-eyed.
and $(WX)Y$, 50 per cent. red-eyed males,
and $(wX)Y$, 50 per cent. white-eyed males.

The second case is illustrated pictorially in Fig. 533.

Examples of sex-linked inheritance in man are colour-blindness and hæmophilia ; these are borne by the X-chromosome and are recessive characters, hence they are carried by the female to a portion of the male descendants, but the females do not

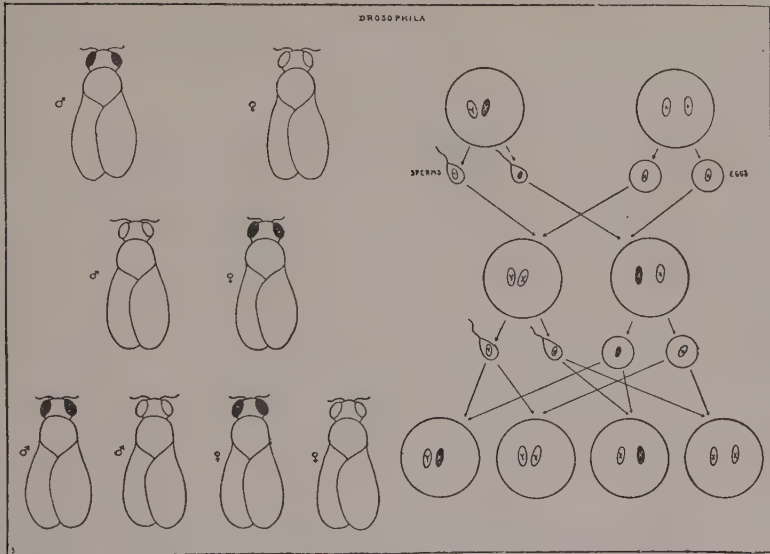


FIG. 533. Sex-linkage in *Drosophila*. Three successive generations at left : red eyes shown in black. The history of the sex-chromosomes through three generations shown at right. X-chromosome of original male in black. (SHARP, after MORGAN.)

themselves suffer from the condition, unless both their parents were affected, or the father affected and the mother a carrier.

Linkage exists between various other pairs of characters, and the inference is that the genes concerned in the transmission of linked characters must be situated on the same chromosome, and hence be transferred together. The evidence for this, which is again chiefly derived from *Drosophila*, is that there are only as many independent factor-pairs as there are chromosomes in the gamete, or somatic chromosome-pairs. Hence, we conclude that the genes connected with a particular group of characters are located on a particular chromosome. From evidence derived from the detailed study of the phenomenon of crossing-over, it is further believed that for each gene is reserved a particular place in the chromosome, like each bead in a necklace, and this position is faithfully retained in the ensuing generations.

Crossing-over. Although many phenomena of heredity are explainable on the supposition that the genes of a chromosome retain their positions relative to one another from generation to generation, thus giving rise to linkage, yet it appears that this does not always apply as regards the two chromosomes of a somatic pair, carrying therefore similar, though not identical, genes. Let us suppose that, in such a pair, we have two series of genes ABCDEFG, etc., and abcdefg, etc. Then, when reduction division occurs

in the formation of the gametes, it may happen that an interchange occurs, so that the gametes may be ABCdefg, etc., and abcDEFG, etc. (Fig. 534).

When this happens, although the linkage persists, there is a certain percentage of departures from the simple Mendelian law of independent association, and it is clear that the further apart on the chromosome any two genes are placed, the more likely will the exchange be to occur.

From the frequency with which this phenomenon of crossing-over happens for particular characters, their relative distance apart on the chromosome has been estimated, and gene-maps of the chromosomes deduced. Double crossing-over also occurs, e.g. ABcdeFG, owing to twisting and cleavage having occurred twice in the process of reduction division. These interesting phenomena belong to the special subject of heredity and genetics and cannot be further discussed here.

Mutation. All breeders of animals and plants are aware that, occasionally, a new feature will suddenly appear and be transmitted thenceforward as an hereditary character. These spontaneously appearing characters are called mutations. On the basis of

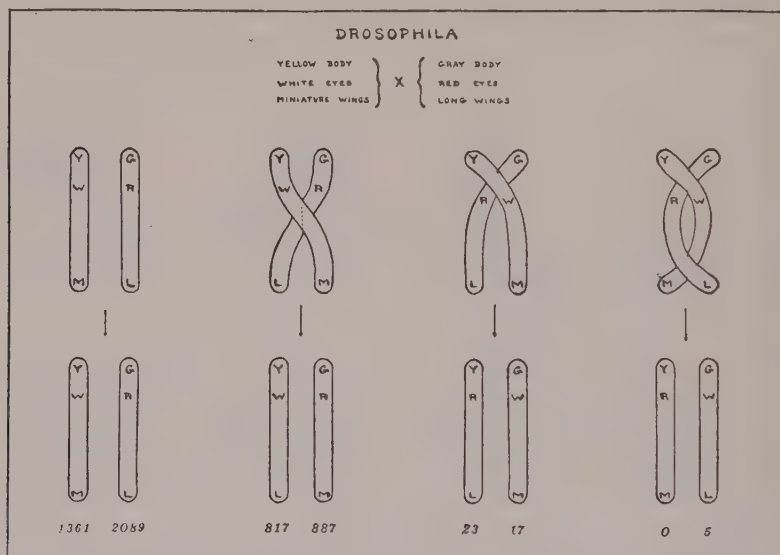


FIG. 534. Diagram to show Formation of New Linkage Groups by Single and Double Crossing-over. (From SHARP, after MORGAN.)

the gene hypothesis, mutation would be regarded as due to some stable alteration in the properties of the gene concerned. We are in complete ignorance as to how these mutations are brought about, so that we cannot, by any means known at present, produce a given mutation, though we can utilise those which occur spontaneously so as to retain the new quality in the breeding of subsequent generations. It has been shown that by the action of X-rays, mutations in *Drosophila* can be made to happen about 150 times as frequently as in nature, and this observation opens up further possibilities of exploring, and perhaps ultimately of controlling, this process.

In other instances, mutations have been shown to be associated with a change in the number of chromosomes: this occurs in some plants; thus Gates has found mutants of *Enothera* with 15, 20, 21, 22, 23, 27, 28, 29 and 30 chromosomes.

REPRODUCTION IN MAN AND OTHER MAMMALS

HORMONIC INFLUENCES IN THE DEVELOPMENT OF THE REPRODUCTIVE ORGANS

A very clear example of chemical correlation is found in the influence exerted by the genital glands upon the other parts of the reproductive

apparatus and upon the body generally. Thus, castration, *i.e.* removal of the testes or ovaries, if carried out before the time of puberty, prevents the development of the secondary sexual characters, which normally occurs at this epoch, in both sexes. Puberty denotes the period at which ripe spermatozoa and ova are produced in the testis and ovary respectively. In the human species, this period is marked, or preceded, in the male by increased growth of the skeleton, by growth of the larynx, leading to a lowering in pitch of the voice, by the growth of hair on the face and pubes, and by the development of sexual desire. In the female, at puberty we find enlargement of the breasts, attended by some growth of the mammary glands and by a moulding of the whole form, making it more fit for the bearing of children. The chief sign of puberty in the female consists in the periodic changes in the uterus, which give rise to menstruation, *i.e.* a flow of blood and mucus from the genital organs, lasting three to five days and repeated about every four weeks. Menstruation persists so long as the ovary is functional and is producing ripe ova. The activity of the ovary comes to an end between the forty-fifth and fiftieth year ('the climacteric' or 'change of life'). With the cessation of its activity, menstruation also stops, and the uterus undergoes a process of atrophy. These secondary sexual characters must be ascribed to the influence of chemical substances produced in the ovary and testis respectively. Castration after puberty, though not causing any change in the skeleton, which has already assumed its permanent form, brings about retrogressive changes in the other genital organs, analogous to those occurring in the female at the climacteric. In animals, the series of changes known as the oestrus cycle, one phase of which includes the phenomena of 'coming on heat' is analogous with the menstrual cycle in the human female, and, like this, depends on the normal activity of the ovary. It is permanently abolished by extirpation of the ovaries, but may be reinduced by implantation in the peritoneum of an ovary from another animal of the same species. This fact shows that the changes in the uterus responsible for 'heat' as well as for menstruation are independent of any nervous connections between the ovaries and the rest of the body, and must therefore be brought about by the circulation in the blood of specific chemical substances produced in the ovaries. According to some authors, the essential factors for the production of these genital hormones are the 'interstitial cells' found in both the testes and ovaries of various animals. These interstitial cells are not, however, universally present.

The chemical correlations between the ovaries and the other organs concerned in reproduction are perhaps best marked in the changes which attend pregnancy. This is accompanied by a great development, first of the mucous membrane, and later on of the muscular wall, of the uterus. The mucous membrane thickens, and so forms a bed for the developing fertilised ovum. With this growth of the uterus, there is a corresponding growth of the other parts of the genital tract, *e.g.* the vagina. At the same time, rapid changes take place in the mammary glands. These changes may be studied experimentally in the rabbit, in which gestation lasts only about thirty days. In a virgin rabbit of a year old, it is difficult, with the naked eye, to see any trace of the mammary gland in the tissue lying under the nipples. Each gland is limited to an area not more than 1 cm. broad, and consists entirely of ducts lined with a single layer of flattened epithelial cells. Four or five days after fertilisation, when it is still impossible with the naked eye to discover any embryos in the swollen uterine horns, on reflecting the skin from the abdomen each mammary gland appears as a circular pink

area, about 3 cm. in diameter. On section, the gland consists of ducts which are in an active state of proliferation, their epithelial lining being two or three cells thick and presenting numerous mitotic figures. By the ninth day, the whole abdomen is covered with a thin layer of glandular tissue; by the twenty-fifth day, this tissue is $\frac{1}{2}$ cm. in thickness and consists for the greater part of secreting alveoli. At full term, the alveoli contain ready-formed milk.

This hypertrophy of the mammary glands during pregnancy occurs after complete division of all possible nervous paths between the glands and the ovaries or uterus. In the guinea-pig, a mammary gland has been actually transplanted to another part of the body, thus severing all its normal nervous connections and yet it enlarged as usual during a subsequent pregnancy. Ancel and Bouin have brought forward evidence that the corpus luteum—the tissue produced in the ovary as a result of the discharge of an ovum—is intimately concerned with the growth of the mammary glands, and may indeed cause a certain degree of hypertrophy of these glands in the entire absence of any product of conception within the uterus.* The limited growth of the glands which occurs at puberty must be connected with the growth of ripe ova or, as suggested by the two French authors, with the growth of the tissue of the corpus luteum resulting from the discharge of ova.

There seem also to be obscure relationships between the activity of the sexual organs and that of certain endocrine organs. Thus, castration at an early age leads to persistence of the thymus gland, which normally atrophies just before the sexual organs commence their functional activity. The existence of a connection between the thyroid and the ovaries has been a popular belief for 2000 years. In many individuals, the thyroid is perceptibly enlarged at each menstrual period. On the other hand, extirpation of the thyroid before puberty brings about, among the other signs of cretinism, failure of development of the ovaries, so that puberty is partially or completely delayed. Hypertrophy of the pituitary body in pregnancy and in menstruation, and enlargement and increase of oxyphile cells in its anterior lobe after castration, as well as the inhibited development of the external genitalia in hypo-pituitarism, illustrate a relation between the pituitary body and the sex glands. There are also close relations with the suprarenal cortex, as shown, for example, in the sexual precocity associated with tumours of that tissue.

THE MALE REPRODUCTIVE ORGANS

In all the higher animals, we may divide the reproductive organs into the essential organs, which form the germ cells, the spermatozoa and ova respectively, and the accessory organs, which have as their office the facilitation of the access of the spermatozoa to the ova (fertilisation), and in the female the nutrition of the product of fertilisation during the early period of its development.

The essential sexual organ of the male is represented by the testis. This is made up of a collection of convoluted tubules, the seminal tubules, which are contained in a number of compartments separated by fibrous septa. The tubules present few or no branches, each one being about 500 mm. long. Several tubules unite to form a straight tubule, which leads by a series of communicating spaces, the rete testis, into the vasa efferentia (Fig. 535). These join to form the duct of the epididymis, coiled into a mass lying at the back of the testis. The epididymis is composed of the convolutions of this single duct, which is about 20 feet long. From the lower end of the epididymis, the vas deferens, a tube with thick muscular walls, leads by the abdominal

* As first shown by Heape, discharge of an ovum and formation of a corpus luteum occur in the rabbit only as a result of copulation. The same effect may be produced by artificial rupture of a ripe follicle, whereupon there is a development of the mammary glands. If no impregnation has taken place (*e.g.* if the buck has been sterilised by ligation of the vas deferens), the glands develop for fourteen days and then begin to atrophy. This period corresponds to the period of active growth of the corpus luteum.

ring to the base of the bladder, where it opens into the beginning of the urethra in its prostatic part. Just before it joins the urethra, each vas deferens presents a diverticulum, the seminal vesicle, which lies along, and is attached to, the base of the bladder. The prostate itself, which surrounds the first part of the urethra, is composed of a matrix of unstriated muscular fibres, enclosing numerous branched racemo-tubular glands. From the point of entry of the vasa deferentia to its orifice, the urethra represents a common passage for the urine and semen. It passes, therefore, through tissues, forming the penis, which is especially adapted for the introduction of the semen into the female. In the urethra we distinguish the prostatic, the membranous and the penile portions. Into the beginning of the penile portion, the bulb of the urethra, open the ducts of the two glands of Cowper. In the penis itself, the urethra is surrounded with erectile tissue, forming the corpus spongiosum, and lies between the two corpora cavernosa, which consist of the same kind of tissue. The erectile tissue is a spongy meshwork of elastic and unstriated muscle fibres, enclosing spaces in free communication with the efferent veins of the organ. The arterioles also open into these spaces, but under normal circumstances both the arterioles and the muscle tissues of the framework are

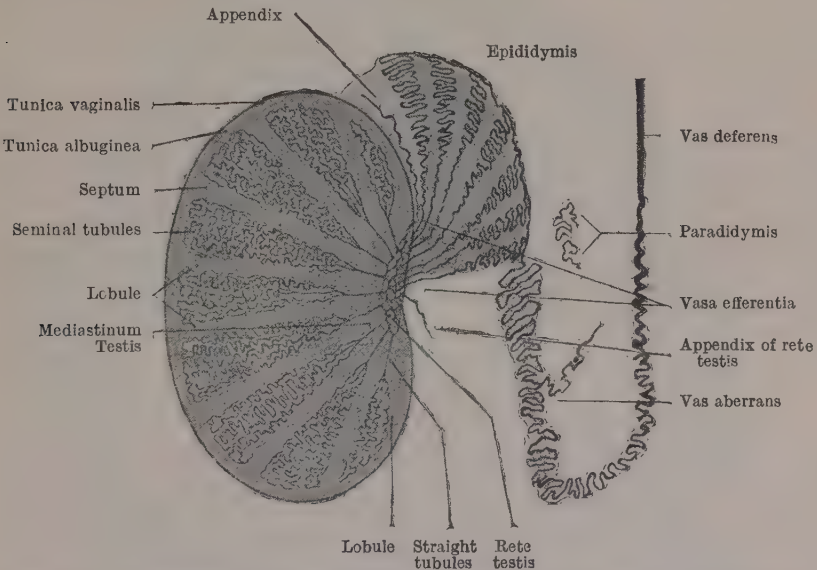


FIG. 535. Diagrammatic Representation of the Course of the Seminal Tubules in the Testis and Epididymis. (After NAGEL.)

contracted, so that the blood trickles very slowly from the arterioles into the spaces, whence it escapes readily by means of the veins. If these muscle fibres be relaxed, so that blood can pass rapidly into, and distend, the spaces, the tissue swells and becomes harder, causing 'erection' of the organ.

In the immature testis, *i.e.* from birth up to puberty, the seminal tubules are filled with cells having large nuclei. Some of these are the spermatogonia, the mother cells of the future spermatozoa, while the others form the cells of Sertoli, whose function it is to act as nurse cells to the developing spermatozoa. The actual formation of spermatozoa begins at puberty, when the spermatogonia divide many times to form the spermatocytes, which in their turn undergo heterotype mitosis to form the spermatids, as already described. By a modification of the latter, the fully developed spermatozoa are formed. These, when mature, pass by the tubules of the testis into the epididymis, where they are stored until an ejaculation takes place, or failing that, die and are reabsorbed. Their movement is probably facilitated by the cells lining the tubule of the epididymis, as well as by the secretion of the lining membrane of the seminal vesicles. It has been stated that the sperma-

tozoa are practically motionless while in the seminiferous tubules of the testis, but become actively motile in the vas deferens, or when mixed with prostatic secretion. It is difficult to understand how the spermatozoa are conveyed through the resistance which must be offered by the huge length of the tubule of the epididymis, unless their onward motion is facilitated by the cilia-like structures attached to some of the cells lining this tubule. The formation of the spermatozoa is continuous, though the rate at which this occurs is variable and is regulated by the sexual activity of the individual. In the fully formed semen, the spermatozoa originating in the testis are mixed, not only with the fluid secreted by the lining membrane of the epididymis and of the seminal vesicle, but also with the mucous secretions of the prostatic glands and of Cowper's glands. Nevertheless, it contains spermatozoa in enormous numbers, the semen emitted at a single act of coitus containing as many as 226,000,000 spermatozoa. Though the vast majority of these are probably capable of fertilising an ovum, this act is carried out by only one—a fact characteristic of the prodigality of nature when dealing with the perpetuation of the type.

INTERNAL SECRETION OF THE TESTIS. Between the seminiferous tubules are groups of so-called *interstitial cells*, which appear to have an important relation to the sexual life of the individual. Removal of the testes before puberty prevents the development of the secondary sex characters; ligature of the vasa deferentia, which is followed by complete degeneration of the seminiferous tubules, but not of the interstitial cells, does not have this consequence. Hence it is assumed that the development of these characters is to be ascribed to the formation, by the interstitial cells, of an internal secretion having that influence on the individual. This is supported by the observation that when testis grafts are made into castrated animals, the male secondary sex characters develop in the usual way. Masculinisation of ovariectomised females has also been claimed to occur when testis substance is grafted.

THE FEMALE REPRODUCTIVE ORGANS

The essential organ of reproduction in the female is the ovary, the seat of production of the ova. The accessory organs in the mammal include the oviducts or Fallopian tubes, the uterus, in which the fertilised ovum is retained during the period of pregnancy, in which it develops, and the vagina, which is adapted for the reception of the penis in the act of copulation.

Among the accessory organs we may also reckon the mammary glands, which undergo a special development during pregnancy, and serve for the nourishment of the young individual during the first period of extra-uterine life.

OVULATION. At birth the ovary consists of a stroma of spindle-shaped cells, and is covered by a layer of cubical epithelium (the germinal epithelium) continuous with the mesothelium lining the general peritoneal cavity. Embedded in the stroma, but especially numerous just underneath the epithelium, are a vast number of 'primordial follicles.' These are formed, during foetal life, by downgrowths of the germinal epithelium. Of the cells prolonged in this way from the germinal epithelium, some undergo enlargement to form the primordial ova, while the others are arranged in a single layer of flattened nucleated cells, the 'follicular epithelium,' as a sort of capsule to the ovum. Of the primordial follicles, about 70,000 are to be found in the ovary of the newborn child, and during the woman's life some 500 of these follow their full course and become ripe ova. During the first twelve to fourteen years of life, although some primordial follicles are constantly developing into well-formed Graafian follicles with growth of the ovum, these do not attain maturity, but retrogress and form 'atretic' follicles. The

maturation of the ovum, with its containing Graafian follicle, first occurs with the onset of puberty. This and other changes which are characteristic of puberty in the female are probably due to some common cause. The first stage in the growth of the follicle is a proliferation of the follicular epithelium, the cells of which become cubical and are arranged in several layers round the ovum. At one point in the mass of cells surrounding the ovum, a cavity appears, filled with fluid, the *liquor folliculi*. The epithelium thus becomes separated into two parts, viz., the *membrana granulosa*,

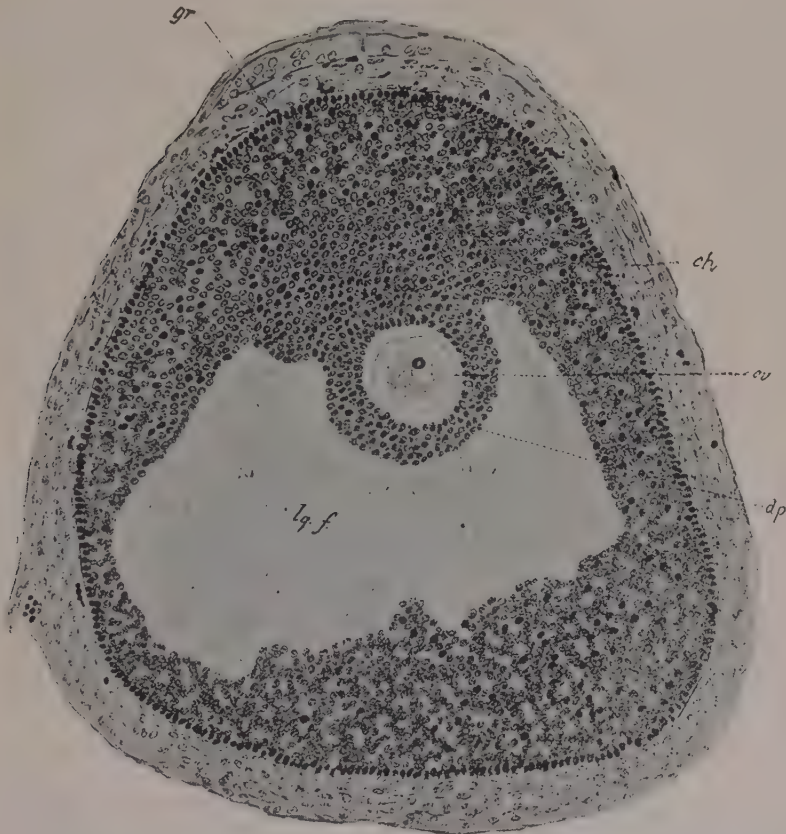


FIG. 536. Graafian Follicle of Mammalian Ovary. (PRENANT and BOUIN.)

ov. Ovum.	ch. Theca.
dp. Discus proligerus.	gr. Membrana granulosa.
lg. f. Liquor folliculi.	

several layers thick, lining the whole follicle, and the *discus proligerus*, a mass of cells attached to one side of the follicle, in which is embedded the ovum (Fig. 536). Round the growing follicle, the stroma assumes a concentric arrangement and forms a capsule, of which the internal layer consists chiefly of spindle-shaped cells richly supplied with blood vessels, while the outer layer—the *theca externa*—is made up of a tough fibrous tissue. With the growth of the follicle, the ovum also becomes larger and surrounds itself with a distinct membrane, known as the *zona pellucida*. This membrane presents a fine radial striation, which is supposed to indicate the existence of canals, through which the ovum can obtain sustenance from the surround-

ing cells of the follicular epithelium. The nucleus also becomes larger, and forms the *germinal vesicle*, containing a well-marked nucleolus—the *germinal spot*. The mature Graafian follicle projects from the surface of the ovary as a transparent vesicle about the size of a pea. (Its diameter is about 15 mm. in the human.) In the process of growth, the ovum has increased from a diameter of 25μ to 200μ . Before the ovum can undergo fertilisation, the double division of the nucleus, or germinal vesicle, has to take place, which leads to the formation and extrusion of the two polar bodies. This process probably occurs just before or just after the discharge of the ovum from the ovary.

With increasing size of the Graafian follicle, the membrane covering it becomes progressively thinner and more vascular, and the ovum moves towards its outer surface. At certain periods, or under certain conditions,



FIG. 537. Fully Developed Corpus Luteum of the Mouse. (SOBOTTA.)

the membrane ruptures, and the liquor folliculi, with the ovum, is discharged into the peritoneal cavity, the ovum being, at first, still surrounded by an adherent mass of the cells of the *discus proligerus*. In some animals, this process of *ovulation* occurs at definite periods of the year. In others, such as the rabbit, the occurrence of ovulation depends upon coitus taking place during the period of sexual activity. There is fairly satisfactory evidence that ovulation is closely related to the activity of the anterior pituitary body. Thus, Fee and Parkes have shown that, in rabbits, removal of the pituitary prevents the normal ovulation following copulation. We shall have later to discuss the relation of ovulation in the human female to the periodic changes occurring in the other parts of the reproductive apparatus.

The ovum, when set free, is directed into the open end of the Fallopian tube by the current set up by the cilia with which the epithelium is furnished. There may be other directive forces besides this, for, when the ovary on one side is removed, and the Fallopian tube on the other side closed, pregnancy, though less likely to occur, is far from infrequent. According

to Corner, the passage of the ovum along the Fallopian tube occupies three days.

After the discharge of the ovum, the remaining portions of the follicle undergo a characteristic series of changes, which results in the production of the *corpus luteum*. Immediately after the rupture, the cells of the membrana granulosa rapidly increase in size, a few of them undergoing mitotic division, so that a dense mass of cells is formed, nearly filling the original follicle. At the same time, the cells of the internal theca proliferate at the periphery, and the cells thus formed also grow in among the cells filling the Graafian follicle. The luteal cells finally attain a size four or five times that of the cells of the membrana granulosa in the mature follicle. Blood vessels grow from the external theca towards the centre of the follicle. The corpus luteum, as the body so formed is called, attains its greatest size in the human about the nineteenth day of the menstrual cycle, at which stage it has a grey colour: it then gradually undergoes regressive changes. The cells within the follicle then undergo fatty degeneration and present a yellow colour, due to a lipochrome known as *lutein*. If, however, the ovum, which has been discharged, undergoes fertilisation, and pregnancy results, the corpus luteum continues to grow for a considerable time and attains its largest size at about the third month, though it persists until after the end of pregnancy. The big corpus luteum found in pregnancy is often spoken of as the 'true' corpus luteum, and is distinguished from the *corpus luteum spurium* of menstruation, or of ovulation without fertilisation. There is no essential difference, other than that of size, between these two kinds of corpora lutea.

It must not be imagined that all the 70,000 primordial follicles found in the ovary of a newborn child undergo this series of changes; it is probable that, in the human female, ovulation occurs, as a rule, alternately in each of the two ovaries, once every four weeks during the thirty-five years of sexual life. A vast number of the Graafian follicles, after developing to a certain extent, undergo regressive changes, both during childhood and during adult life. The cellular elements degenerate, leucocytes wander into the follicle and attack the degenerating ovum, so that finally the follicle is replaced by connective tissue, without the formation of any corpus luteum.

THE ŒSTROUS CYCLE

The sexual activity of females shows recurrent changes, which vary in detail according to species, the whole cycle being known as the œstrous cycle. In some animals, known as monœstrous, such as the bitch, there is only one œstrous period in each sexual season, of which the bitch has two a year, and between the seasons a period of quiescence, the anœstrus, is found. In others, *e.g.* mare, pig, rat and mouse, there are several heat or œstrous periods in the season, and these are separated by short resting intervals called diœstrus. The phases of the œstrous cycle may be classified as follows:

- (1) Anœstrus (or diœstrus) sexual rest.
- (2) Pro-œstrus, the preparatory phase.
- (3) Œstrus, the period of 'heat,' during which alone, in most animals, copulation is permitted.
- (4) Metœstrus, or pseudo-pregnancy, or true pregnancy.

These periodic modifications of sexual activity are accompanied by changes in the generative organs, in general metabolism and activity (œstrus being accompanied by increase of general activity), as well as in the behaviour

towards the male, and these have been extensively studied during the last few years.

The recurrent changes in the generative organs affect the external genitalia, the vagina, uterus, ovaries, and often (especially during pseudo-pregnancy) the mammary glands, and these changes are closely related to the normal sexual life in any given species. It is simplest to regard the œstrous cycle as made up of a basic ovarian cycle, consisting of a short diœstrus, a pro-œstrus and an œstrous period, with a short transition phase of post-œstrus (or metœstrus); and such a basic cycle is well seen in the unmated mouse. In most other animals, and in the mated mouse, the cycle is further modified by factors introduced by the greater development of the corpus luteum, which, in the unmated mouse, is small and transient.

During pro-œstrus, growth of the ovum occurs, and at œstrus, in most animals, maturation and ovulation follow, though in some, such as the rabbit and cat, this only happens when copulation takes place.

The study of the œstrous cycle has been greatly facilitated by the discovery, made by Stockard and Papanicolaou, that the vaginal lining of some mammals undergoes characteristic histological changes during each phase, so that, by microscopical examination of vaginal smears at regular intervals, the state of the cycle can be determined.

These changes, as seen in the smear, are briefly as follows: During œstrus the vagina is cornified, during meta-œstrus leucocytes appear in the smear, during dioœstrus there are leucocytes and nucleated epithelial cells, and in the pro-œstrous period there are nucleated epithelial cells only. The whole cycle in the unmated mouse takes, on an average, 5·7 days (Parkes), occupied approximately as follows: Pro-œstrus, eighteen hours; œstrus, forty-two hours; metœstrus, twelve hours; dioœstrus, two and a half to three days. In the pig, there is, at intervals of three weeks, an œstrous period lasting three days.

If both ovaries are removed the œstrous cycle ceases, either at once or after one more period. In the mouse it may, however, recommence, owing to regeneration of ovarian tissue (Parkes, Brambell and Fielding). The œstrous cycle also ceases during pregnancy and in some animals during lactation.

The Causation of œstrus. It has often been supposed that the maturation of the Graafian follicles was the prime mover in bringing about the condition of œstrus, but Parkes has recently shown that the œstrous cycle persists as in the normal animal, after the total obliteration of the follicular system by exposure to X-rays, either before, or at any time after, birth. It is clear, therefore, that although the presence of the ovary is essential, the presence of the ripening follicles is not. This is further borne out by the observation (Brambell and Parkes) that in those cases where there was one last œstrous period following double oöphorectomy, the follicles of the ovaries removed had not yet reached maturity. This suggests that, instead of ovulation being the cause of œstrus, they must both have some common cause, and there is clear proof that this is a hormone.

The œstrus-producing Hormone. This was first demonstrated by Adler in 1912, in ovary extracts, and it was clearly shown in 1923 by Allen and Doisy that an œstrus-producing substance was present in the liquor folliculi. In cow or pig ovaries, this can be obtained in sufficient amount to enable the effect of extracts to be tested on oöphorectomised rats or mice, using the vaginal smear method to identify the effects. The same, or a closely similar hormone, can be extracted from the solid parts of the ovary, and also from the placenta. The extracts are prepared by treatment with alcohol, evaporation of the

extract, re-extraction with ether, acetone, with strong alcohol, and finally with methyl alcohol. The substance, which has been called *œstrin* by Parkes, appears to be almost insoluble in water, and associated with fats and lipides. When emulsified with water and administered subcutaneously to oöphorectomised mice, œstrus is induced in the course of the second day. The extract is standardised by the use of this method, one mouse unit being defined by Coward and Burn as the amount which will induce œstrus in 50 per cent. of oöphorectomised mice. With larger doses, it is found that the duration of the effect is in linear relationship to the amount of œstrin given, the effect with large doses lasting for many days. The following table shows the yield of the substance from various sources :

Source.	Yield in mouse units per Kilogram.	Observer.
Liquor folliculi :		
Human	433—7000	Allen, Pratt & Doisy.
Cow	37—788	Parkes & Bellerby.
Whole ovaries :		
Cow	73—350	Parkes & Bellerby.
Corpora lutea :		
Solid	Nil.	Parkes & Bellerby.
Hollow	11	Parkes & Bellerby.
Fluid from hollow	184	Parkes & Bellerby.

The œstrin preparations obtained from various sources by different workers exhibit very different degrees of activity. Parkes and Bellerby, for instance, have prepared, from cow's liquor folliculi, extracts of which 3 to 12 mg. contain one mouse unit ; from that of the pig 14 to 21 mg., and from whole ovaries extracts which were about half as active weight for weight. Placenta gave extracts of about the same activity as the ovary. It is obvious from such results, that these extracts are contaminated with impurities.

The substance is not species-specific, but there is no definite information as regards its chemical nature.

The large amounts of the œstrus-producing substance in the placenta, and its presence also in the liquor amnii, are puzzling features.

It might be supposed, from the high concentration of œstrin in the liquor folliculi, that the substance was manufactured in the follicle, but this need not be so. The occurrence of œstrus in animals deprived of follicles by exposure to X-rays rather suggests that the hormone is normally produced in the stroma of the ovary. As regards its high concentration in the placenta, it is evident that, owing to the size of this organ, the placenta contains far more œstrin than both ovaries ; it has been suggested that the placenta takes up the hormone from the blood, and so protects the foetus from its effects. The fact that the administration of large amounts of œstrin to pregnant animals leads inevitably to abortion, certainly suggests that it is not normally present in the free state in pregnant animals.

The main effect of the injection of an adequate dose of œstrin into the oöphorectomised female is the onset of the uterine and vaginal changes characteristic of œstrus, and also, in some cases, a slight and transient enlargement of the mammary glands. The uterus enlarges, becomes hyperæmic, and, it is stated, shows more powerful rhythmic contractions. Injection of œstrin does not cause follicular maturation. The production of the hormone and

ovulation, though due to a common stimulus, and normally coincident, are mutually independent.

If, as indicated above, the ripening of Graafian follicles is not the cause of the presence of œstrin, how are we to explain the periodicity of œstrus, or the occurrence at puberty of the first œstrous cycle? Recent work by Smith and Engle gives support to the view that the advent of puberty, as well as the rhythmicity of the œstrus phenomena, are part of an endocrine phenomenon, in which the anterior pituitary plays an important, or even a determining, rôle. Injection of suspensions of the anterior lobe of the pituitary body into adult females was followed by immediate maturation of large numbers of ova, and, if pregnancy followed, by the formation of abnormally large numbers of foetuses. Injected into immature animals, the suspension brought about precocious œstrus, after a latent period of about three days, *i.e.* a day longer than is required for the effect of an injection of œstrin to manifest itself. Injection into oöphorectomised animals produced no effects, which makes it evident that the effects which are produced are due to an inductive action on the ovary. In partially oöphorectomised animals, however, the hypertrophy of the remaining ovarian tissue is greatly accelerated by administration of the anterior pituitary substance.

Relation of the Corpus Luteum to the Cycle. The basal ovarian cycle is modified to a variable extent by the presence of the corpus luteum. The effect of this, in the unmated mouse, is small, in correspondence with the insignificant development of the corpora formed after ovulation. After mating with vasectomised males, the corpora persist for a longer period and attain a greater development, and the period of the cycle is lengthened to about twelve days, during which time the uterus is much enlarged and vascularised, and there is pronounced growth of the mammary glands. This condition is called *pseudo-pregnancy*, and is seen as a normal sequel to the œstrous period in the bitch and other species where the corpora lutea of ovulation persist for a much longer time, irrespective of whether sterile copulation has occurred or not. In normal pregnancy, where the corpora lutea maintain a still greater development, the œstrous cycle is suspended and all the above phenomena are accentuated. Consideration of this and other facts indicates that the corpus luteum has probably the following functions:—

- (1) Inhibition of œstrus and ovulation.
- (2) Sensitisation of the uterus.
- (3) Maintenance of pregnancy.
- (4) Enlargement of the mammary glands during pregnancy and pseudo-pregnancy.

The inhibition of œstrus and ovulation which is effected by the agency of the corpus luteum can be shown in a variety of ways. Thus, in the cow and guinea-pig, the removal of the corpora lutea of ovulation hastens the onset of the next cycle: conversely, if luteal formation is augmented, as H. M. Evans found to happen after injection of caustic soda extracts of anterior pituitary, there is a cessation of the œstrous cycle, together with other changes characteristic of pseudo-pregnancy.

This action of the corpus luteum is apparently also due to a hormone, and Parkes and others have recently been able to prepare from cow's corpora lutea extracts which have an œstrus-inhibiting action, *i.e.* which suspend œstrus in the normal animal. In conformity with this, it was found that when œstrin in sufficiently large doses was administered to lactating animals, œstrus was induced.

The same, or a different, hormone, also derived from the corpus luteum, appears from the work of Fränkel to be essential for the preparation (sensitisation) of the endometrium for the attachment of the fertilised ovum, thus initiating pregnancy. It was shown by Loeb that, in the guinea-pig, mechanical irritation of the uterine mucosa, *e.g.* by a small piece of glass capillary, led to local accumulation of decidual cells, which represented the attempted formation of a placenta; but after removal of the corpora lutea, this response vanished.

Even after the placenta has been fully formed, however, the corpus luteum appears to be essential for the continuance of pregnancy, and removal of the corpora, or of the entire ovary, is followed by abortion. As a still clearer demonstration that this effect of oöphorectomy in pregnancy is not due to the removal of other ovarian hormones, the following experiment by Parkes may be quoted. He destroyed the follicular tissue of one ovary, in mice, by X-rays, and the animals were then mated and became pregnant: when the normal ovary, which alone contained corpora lutea, was removed, abortion followed, although it was shown by separate experiments, that the remaining X-rayed ovary was able to carry out normal ovarian hormonal functions, such as the production of oestrus.

MENSTRUATION.

Puberty in the girl is marked by the onset of menstruation. Under this term is understood a flow of blood and mucus from the uterus, which recurs about every four weeks and lasts each time from four to five days. Menstruation is suspended during pregnancy and lactation. Before the first menstrual period, other signs of puberty, *i.e.* of approaching sexual maturity, are usually observed and are attributed to the elaboration, by the ovary, of an internal secretion. These include rapid growth, with changes in the skeleton, leading to the typically feminine type of pelvis, a development of the mammary glands, and the growth of hair on the pubes. At the same time, there is increased development of the mental characteristics which are typical of the sex. The amount of blood lost at each menstrual period varies between 100 and 300 grammes. During the 'period' there are often disturbances of other functions of the body, and at the same time there is a general disinclination for exertion.

In describing the menstrual cycle, it is customary to number the days from the commencement of one flow to the commencement of the next. The histological changes, as described by Shaw, are briefly as follows: By the tenth day the mucosa, or endometrium, is 2 mm. thick and in a resting condition similar to that after the menopause. The cells are low columnar and the glands are short simple tubules, between which are fusiform stroma cells. Preparation for menstruation begins about the fourteenth day, with nuclear division in the gland cells, hypertrophy of the tubules and swelling of stroma cells. The enlargement of gland tubules increases until the twentieth day, when the oedema of the stroma becomes localised to the middle zone of the endometrium, and the capillaries become dilated. From the twentieth to the twenty-eighth day, the pre-menstrual changes become more apparent: the superficial zone, with close-packed stroma cells, closely resembles the compact layer of the decidua, while the middle zone, with dilated glands and oedematous stroma, resembles the spongy layer. The endometrium is now about 6 mm. thick. When the flow begins, these two outer zones become disorganised, infiltrated with leucocytes and phagocytes, and ultimately are shed, with some bleeding, leaving the basal zone containing the ends of the glands with the stroma bare. After the flow, the epithelium from these glands grows over the bare stroma to form a lining, and the endometrium is thus restored to a resting condition by the tenth day of the next cycle.

THE RELATION OF OVULATION TO MENSTRUATION. There is no doubt that menstruation depends on the functional activity of the ovary. Its onset coincides with the first production of ripe ova in the ovary, and it ceases, with the cessation of ovulation, at the climacteric or menopause. In cases where the ovaries have been removed before puberty, menstruation never occurs. Removal of both ovaries during adult life generally brings about a premature menopause. It seems probable that the ripening and discharge of the ova in the human ovary occurs about the thirteenth to seventeenth day of the menstrual cycle. But there has been much division of opinion as to the exact relation between the two processes, since it is only among the primates that any process resembling menstruation occurs.

In the human menstrual cycle we cannot speak of 'œstrus.' The female may experience desire at any period of the cycle, and though coitus may be refused during menstruation itself, or for some time after, this is on æsthetic or ritualistic grounds rather than from absence of desire. Evidence as to the relation of ovulation to menstruation is still imperfect and rests chiefly on observations made on the ovaries in abdominal operations, and certain others by Corner on menstruation in the primate, *Macacus rhesus*. These tend to

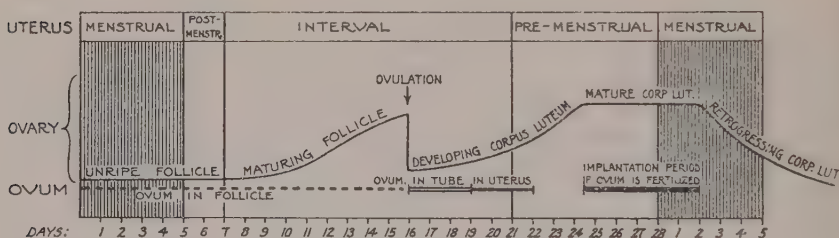


FIG. 538. Course of Events in the Human Menstrual Cycle.
(G. W. CORNER.)

support the view originally put forward by Fraenkel. According to this view, the corpus luteum is an organ of internal secretion, by which the uterus is prepared for the implantation of the fertilised ovum. After ovulation, which takes place once in each menstrual cycle, the corpus luteum at once begins to develop and attains maturity in about five days, *i.e.* about the twenty-first day. It persists in this state until the commencement of the menstrual flow, when it usually abruptly degenerates; in any case, it is already undergoing degeneration by the end of the flow. Coincident with the growth of the corpus luteum, the uterine mucosa undergoes changes preparatory to receiving a fertilised ovum. The premenstrual stage thus corresponds to the post-œstrous or pseudo-pregnancy stage of the lower mammals. If impregnation occurs, the embryo becomes embedded in the thickened membrane, and this continues to grow and to form the placenta, which involves the opening of maternal blood-vessels into large intervillous spaces. Menstruation may be regarded as due to failure of fertilisation to take place. If the ovum is not fertilised, the corpus luteum undergoes retrogression, and, possibly in consequence of this, the hypertrophied mucosa breaks down, the *débris* being discharged, together with extravasated blood, as the menstrual fluid.

The probable course of events in the human menstrual cycle is summarised in the diagram above (Fig. 538).

COPULATION AND IMPREGNATION

The spermatozoa are introduced into the female genital tract by the act of copulation, or coitus. After their entry they may come in contact with, and fertilise, the ovum, which is discharged from the ovary by bursting of a Graafian follicle. Before coitus can occur erection of the male organ must take place. The mechanism of erection is twofold. The most important factor, as was shown by Eckhard and Lovén, is an active dilatation of the vessels of the penis, especially of the smaller arteries. If the penis be cut across while in the flaccid condition, venous blood merely trickles away from the cut surface, whereas, if erection be excited, the flow of blood from the cut surface is increased eight to ten times, and the blood becomes bright scarlet in colour. A second factor is the contraction of the *ischio-cavernosus* or *erector penis* muscles, certain fibres of which pass over the dorsal veins of the penis and compress these vessels when they contract. Since ligation of the veins coming from the penis does not produce erection, the contraction of this muscle must be regarded as simply aiding the effects of the arterial dilatation. It is thus possible to excite erection in an animal, in whom the second factor has been abolished by paralysing the muscles by means of curare.

Before, or at the beginning of, coitus analogous changes occur in the female organs, leading to erection of the clitoris and of the erectile structures of the vulva. The glands of the vulva, especially the glands of Bartholin, secrete a mucous fluid, thus lubricating the passage into the vagina. The friction between the glans penis and the wall of the vagina causes a reflex discharge of motor impulses in both male and female (the 'orgasm'). In the former, the muscular walls of the vasa deferentia and seminal vesicles enter into rhythmic contractions, thus ejaculating the spermatozoa and secretions they contain into the urethra. The spermatozoa, mixed with the secretions of the epididymis, the seminal vesicles, the prostatic glands, and the glands of Cowper, form the semen, which, at the orgasm, is ejaculated from the urethra by rhythmical contractions, from behind forwards, of the bulbo- and ischio-cavernosi muscles. It has been stated that movements take place coincidentally in the uterus, so that its axis more nearly corresponds to that of the vagina. The female orgasm, however, does not play an essential part in impregnation, which, as shown by Spallanzani in the eighteenth century, can be effected by artificial insemination, *i.e.* injection of semen into the vagina by a syringe. The movement of the semen along the uterus and Fallopian tubes is ascribed by certain observers to an antiperistaltic contraction of these organs. A more important factor is probably the movement of the spermatozoa themselves. As we have already seen, these are introduced into the female passage in countless numbers. They will be chemiotactically attracted by the alkaline mucus, secreted by, and filling, the cervix of the uterus. When they have entered this organ they will meet the downward stream of mucus impelled by the action of the cilia lining the uterus and Fallopian tubes. It seems probable that their reaction to this current is to swim * against it (*positive rheotaxis*), so that they reach the upper part of the Fallopian tubes, or the surface of the ovary itself. Fertilisation of the ovum normally occurs in the Fallopian tube, and the fertilised ovum is then carried slowly down the tube into the uterus.

* Spermatozoa move in a straight line, at the rate of 2 to 3 mm. per minute. Thus they might traverse the distance of 16 to 20 cm. between the os uteri and the trumpet-shaped orifice of the Fallopian tubes in three-quarters of an hour. In animals, spermatozoa have been found at the peritoneal end of the Fallopian tubes within an hour or two after coitus.

NERVOUS MECHANISM OF COITUS. Although, in both sexes, coitus is attended by a high degree of psychical excitement, yet it can be carried out when all impulses from the higher centres are cut off by section of the cord in the dorsal region. The centre presiding over the act is situated in the lumbar spinal cord. The external generative organs, like the bladder, are supplied from two sets of nerve fibres—from the lumbar nerves through the sympathetic, and from the sacral nerves. The fibres from the lumbar nerves arise, in the cat, from the second, third, and fourth, or the third, fourth, and fifth lumbar nerve roots, and, in the dog, from the thirteenth thoracic, and the first to the fourth lumbar roots. They run in the white rami communicantes to the sympathetic chain, whence they may take one of two paths.

(a) The great majority of the fibres run down the sympathetic chain to the sacral ganglia, whence fibres are given off in the grey rami communicantes to the sacral nerves; their further course is by the pudic nerves, none running in the *nervi erigentes*.

(b) A few fibres go by the hypogastric nerves to the pelvic plexus.

Excitation of these fibres causes contraction of the arteries of the penis, and of the unstriated muscles of the tunica dartos of the scrotum. In animals which possess a retractor penis muscle, excitation of the lumbar nerves causes strong contraction of that muscle. The effect of stimulation of these nerves is, therefore, to inhibit erection.

The fibres from the sacral nerves can be divided into two classes—visceral and somatic. The visceral branches run in the pelvic nerves, or *nervi erigentes*. Stimulation of these fibres produces active dilatation of the arteries of the penis or vulva, and also inhibition of the unstriated muscle of the penis, of the retractor muscle of the penis, when present, and of the vulva muscles. The somatic branches supply motor nerves to the ischio- and bulbo-cavernosi, as well as to the constrictor urethræ. In the female, they supply the analogous muscles, namely, the erector clitoridis (ischio-cavernosus) and the sphincter vaginæ (bulbo-cavernosus). Both sets of sacral fibres are therefore involved in the erection of the generative organs which accompanies coitus.

The internal organs, *i.e.* the uterus and vagina in the female, and vasa deferentia, seminal vesicles, and uterus masculinus in the male, differ from the external organs in receiving no efferent nerve fibres from the sacral nerves, as has been pointed out by Langley and Anderson. They are supplied with fibres, which pass out through the anterior roots of the third, fourth, and fifth lumbar nerves (in the rabbit and cat), and run through the sympathetic to the inferior mesenteric ganglia, whence they proceed by the hypogastric nerves. On stimulating these fibres, two effects are produced on the uterus and vagina, namely, a contraction of the small arteries, leading to pallor of the organs, and a strong contraction of the muscular coats.* In the vagina, the contraction can usually be seen to start from one end and spread to the other. The whole then remains for a time in a state of powerful tonic contraction, which affects both longitudinal as well as circular muscles. In the male, stimulation of these nerves excites contraction of the whole musculature of the vasa deferentia and seminal vesicles, which may be strong enough to cause emission of semen from the penis. These effects on the uterus and seminal vesicles are not abolished by injection of atropine.

The course of the sensory fibres which represent the afferent side of the

* Under some circumstances, stimulation of the sympathetic nerves may cause *relaxation* of the uterus, as also may the administration of adrenaline.

arc, from the generative organs to the lumbo-sacral cord has not yet been fully made out, but it seems probable that it corresponds to the course taken by the efferent fibres.

An accessory genital muscle, the *retractor penis*, which is found in the dog, cat, horse, donkey, hedgehog (not in the rabbit or man), presents considerable physiological interest. It consists of a thin band of longitudinally arranged unstriated muscle (15 to 20 cm. long in a spaniel weighing about 15 kilos.), which is inserted at the attachment of the prepuce, and is continued backwards in a sheath of connective tissue to the bulb, where it divides into two slips which pass on either side of the anus. A few striated fibres are found in the posterior part of this muscle, derived from the external sphincter of the anus and the bulbo-cavernosus muscles.

The muscle is innervated from two sources, the two nerves having antagonistic actions (*cp.* p. 192). The *motor* fibres to the muscle are derived from the lumbar sympathetic (*i.e.* the upper set of nerve roots), and run to the muscle in the internal pudic nerve. The pelvic nerves, on the other hand, carry *inhibitory* impulses to the muscle, thus enabling the concomitant vascular dilatation to take effect in producing erection of the penis.

PREGNANCY

Fertilisation of the ovum takes place in the Fallopian tube. In the human subject, fertility is probably highest about a week after the end of menstruation and lowest about a week before its onset. Directly one spermatozoon has penetrated into the ovum, a membrane is formed round the yolk, which prevents the entrance of any other spermatozoa. The fusion of the male and female pronuclei is followed immediately by division of the fertilised ovum, so that, by the time it arrives in the uterus (about eight days after fertilisation), it consists of a mass of cells known as the morula. At this time, the ovum has a diameter of about 0.2 mm. Pregnancy in the human being lasts about nine months, birth generally taking place 280 days, *i.e.* ten periods, after the last menstrual period.

With the arrival of the fertilised ovum in the uterus, extensive changes begin in this and in the neighbouring organs of generation. The virgin uterus is pear-shaped, and its cavity amounts to about 2-5 c.c. Just before birth, the volume of the uterus is about 5000-7000 c.c., and the walls of the organ are thickened in proportion. In the hypertrophy of the uterine wall, all its elements are involved, but especially the muscle cells. It is doubtful whether there is an actual formation of new muscle fibres, but each fibre grows in length and thickness, becoming finally between seven and eleven times as long, and three to five times as thick, as in the unimpregnated uterus (Fig. 539). There is at the same time a great growth of the blood vessels, which have to supply, not only the growing wall of the uterus, but also by means of a special organ—the placenta—the nutritional needs of the developing foetus.

CHANGES IN THE UTERINE MUCOUS MEMBRANE. After conception, the uterine mucous membrane shows a continuation of those

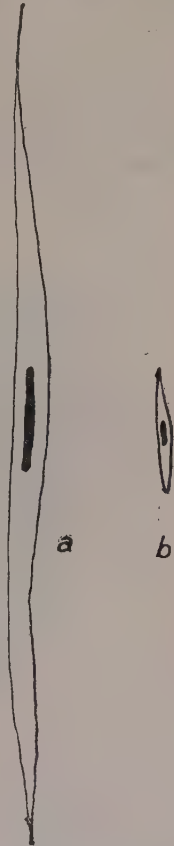


Fig. 539. Isolated Muscle Cells from the Uterus, showing the Hypertrophy during Pregnancy. (After BUMM.)

a. Fibre from uterus in ninth month of pregnancy.
b. Fibre from a non-gravid uterus.

hypertrophic changes which we have seen to occur regularly during the premenstrual phase. Within fourteen days, it has attained a thickness of $\frac{1}{2}$ cm., and by the end of the second month $\frac{3}{4}$ cm. On section, it shows a compact layer, lining the cavity of the uterus, and beneath this, abutting on the muscular tissue, is a spongy layer three times as thick as the compact layer. The superficial epithelium becomes flattened, loses its cilia, and degenerates. In the spongy layer, the uterine glands proliferate, the stroma cells are enlarged, and the blood capillaries are widely dilated. The stroma cells become converted into the large *decidual* cells. By the time the fertilised ovum arrives in the uterus, the process of hypertrophy of the layers of the mucous membrane has already made some progress. As it lies on the mucous membrane, the outermost cells of the developing ovum exercise a destructive influence on the adjacent cells of the mucosa, apparently



FIG. 540. Diagram to illustrate the Imbedding of the Ovum in the Decidua, and the First Formation of the Foetal Villi in the form of a Syncytial *Trophoblast* (derived from the Outer Layer of the Ovum) which is invading Sinus-like Blood Spaces in the Decidua. (After T. H. BRYCE.)

through some sort of digestion, so that the ovum sinks into the membrane and reaches the sub-epithelial connective tissue. Round the margins of the depression which the ovum has made for itself, the mucous membrane grows over the protruding part of the ovum (Fig. 540). When this has taken place, the different parts of the mucous membrane receive different names. Since (in man) they are all to be cast off with the foetus at birth, each part is spoken of as the decidua, that lining the main body of the uterus being known as the *decidua vera*, that covering the protruding part of the egg as the *decidua reflexa*, while that to which the egg is immediately attached is the *decidua serotina* or *basalis*. It is from the latter that the placenta is formed. By the end of the second week, the blood vessels in this situation are considerably enlarged. This enlargement proceeds, affecting especially the capillaries and veins, until these form venous sinuses at the junction between the mucous membrane and the muscular coat. Changes take place at the same time in the embryo. When it sinks into the mucous membrane it has a diameter of 1 mm. The blastoderm is fully formed, with

its three layers ; the yolk sac, the body cavity and the amnion are present. The outermost layer of the epiblast becomes specially modified to serve for the nutrition of the embryo, and gives rise to numerous villi, the chorionic villi, so that the whole ovum has a shaggy appearance. Since this tissue takes no part in the further development of the embryo, but serves simply for its nutrition, it is often spoken of as the *trophoblast*. With the formation of foetal blood vessels, these penetrate into the villi, together with mesoblast. The villi grow into the venous spaces, especially in the basal part of the decidua, so that, at this period, the foetal villi are immersed in maternal blood, the foetal blood vessels being separated from the maternal blood by a double layer of epithelium, one layer of which is maternal and the other foetal in origin. Later, these cells become reduced to a single layer.

NUTRITION OF THE EMBRYO. At the earliest period of its development, the fertilised ovum is dependent for its nourishment on the remains of the cells of the discus proligerus adhering to it, or on the fluid of the Fallopian tube in which it is immersed. The first blood vessels which are formed serve to take up nourishment from the yolk sac. In man, this source of supply is insignificant, and from the second week onwards, blood vessels traversing the chorionic villi come into close relation with the maternal blood, from which, henceforth, the whole growth of the foetus is to be maintained by a special development of these connections in the placenta.

In the fully formed foetus, blood passes from the foetus to the placenta by the umbilical artery, and is returned by the umbilical veins. There is no communication between foetal and maternal circulations. The placenta represents the foetal organ for respiration, nutrition, and excretion. Thus, the umbilical artery carries to the placenta a dark, venous blood, which in this organ loses carbonic acid and takes up oxygen, so that the blood of the umbilical vein is arterial in colour. The oxygen requirements of the foetus are, however, but small. It is protected from all loss of heat, movements are sluggish, or for the most part absent, and the only oxidative processes are those required in the building up of the developing tissues. On the other hand, the foetus has need of a rich supply of foodstuffs, which it must obtain through the placental circulation. It is imagined that the epithelium covering the villi serves as an organ for passing on the necessary foodstuffs from the maternal to the foetal blood, in the form best adapted for the requirements of the foetus. We know, however, practically nothing as to the changes or mechanism involved in this transference. Although most of the organs of the foetus are fully formed some time before birth, they are for the most part in a state of suspended activity. The nitrogenous excreta are turned out by the placenta, so that the foetal secretion of urine is minimal or absent. The alimentary apparatus is almost all practically ready. Thus, pepsin can be extracted from the foetal gastric mucous membrane. The pancreas contains trypsinogen and the intestinal mucous membrane pro-secretin. Amylolytic ferments seem, however, to be absent, both from the salivary glands and the pancreas. The liver stores up glycogen and secretes bile, which accumulates in the small intestine, helping to form the *meconium*. This is generally voided by the child, shortly after birth.

THE FOETAL CIRCULATION. In the foetus, from the middle of intra-uterine life, we find certain arrangements of the circulation which are directed to providing the forepart of the body, especially the rapidly growing brain, with oxygenated blood, while the less important tissues of the limbs and trunk receive venous blood (Fig. 541). The arterial blood coming from the placenta along the umbilical vein can pass directly into the liver. The greater part of it, however, traverses the ductus venosus, to enter the inferior

vena cava, by which it is carried to the right auricle. Here it impinges on the Eustachian valve, and is directed thereby through the *foramen ovale* into the left auricle, whence it passes into the left ventricle, to be driven into the aorta. As this arterial blood passes into the inferior cava, it is of course mixed with the venous blood, returning from the lower limbs and lower part

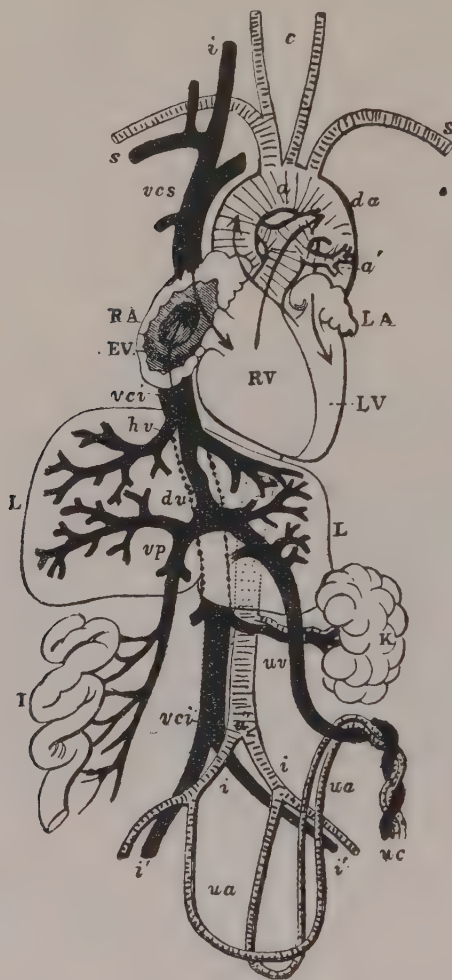


FIG. 541. Diagrammatic Outline of the Organs of Circulation in the Fœtus of Six Months. (After ALLEN THOMSON.)

RA, right auricle of the heart; RV, right ventricle; LA, left auricle; EV, Eustachian valve; LV, left ventricle; L, liver; K, left kidney; I, portion of small intestine; *a*, arch of the aorta; *a'*, its dorsal part; *a''*, lower end; *vcs*, superior vena cava; *vci*, inferior vena where it joins the right auricle; *vci'*, its lower end; *s*, subclavian vessels; *j*, right jugular vein; *c*, common carotid arteries; four curved dotted arrow-lines are carried through the aortic and pulmonary opening and the auriculo-ventricular orifices; *da*, opposite to the one passing through the pulmonary artery marks the place of the ductus arteriosus; a similar arrow-line is shown passing from the inferior vena cava through the fossa ovalis of the right auricle and the foramen ovale into the left auricle; *hv*, the hepatic veins; *vp*, vena portæ; *x* to *vci*, the ductus venosus; *uv*, the umbilical vein; *ua*, umbilical arteries; *uc*, umbilical cord cut short; *ii'*, iliac vessels.

the left auricle, whence it passes into the left ventricle, to be driven into the aorta. As this arterial blood passes into the inferior cava, it is of course mixed with the venous blood, returning from the lower limbs and lower part

of the trunk. By the aorta, this mixture, containing chiefly arterial blood, is carried to the head and fore limbs. The venous blood from these parts is carried by the superior vena cava to the right auricle, and thence to the right ventricle, by which it is driven into the pulmonary artery. Only a small part of the blood passes through the lungs, the greater part traversing the patent *ductus arteriosus* to be discharged into the aorta below the arch, whence it flows partly to the lower limbs and trunk, but chiefly to the placenta by the umbilical arteries. In the foetus, therefore, the work of the circulation is largely carried out by the right ventricle. The greater thickness of the left ventricular walls, which is so characteristic of the adult, does not become evident until shortly before birth.

With the first breath taken by the newborn child, all the mechanical conditions of the circulation are modified. The resistance to the blood flow through the lungs being diminished, the blood passes from the pulmonary arteries through the lungs into the left auricle. The pressure in the left auricle is thus raised, while that in the right auricle falls, so that the foramen ovale is maintained closed. Even before birth, proliferation of the lining membrane may be seen both in the ductus arteriosus and in the ductus venosus; and with the mechanical relief of the vessels afforded by respiration and the changed conditions of the foetus, this proliferation goes on to complete obliteration of the vessels.

PARTURITION

As the uterus increases in size and becomes more distended, its irritability becomes greater, so that it is easily excited to contract. The stimulus for this may be supplied from adjacent abdominal organs, from the brain, as by emotions, or by direct excitation of the internal surface of the uterus, in consequence of movements of the foetus. In many cases, no antecedent stimulus can be discovered, and the automatic contraction of the uterus seems to be analogous to that which occurs in the distended bladder. These contractions ordinarily give rise to no sensations, and are felt only when they are augmented in consequence of reflex stimulation. During the greater part of pregnancy they have little or no effect on the contents of the uterus. During the last weeks or days of pregnancy, however, these contractions, which have now become more marked, have a distinct physiological effect. Not only do they, by pressing on the foetus, cause it, in most instances, to assume a suitable position for its subsequent expulsion, but, affecting the whole body of the uterus, including the longitudinal muscular fibres surrounding its neck, they assist the general enlargement of the organ in dilating the internal *os uteri*, so that the upper part of the cervix is obliterated and drawn up into the body of the uterus some little time before labour has commenced.

With these changes in the uterus are associated changes in the round ligaments and in the vagina and vulva. The muscular fibres of the round ligaments become much hypertrophied and lengthened, and these structures can therefore appreciably aid the uterine contractions in the subsequent expulsion of the foetus. The vaginal walls become thickened and of looser texture, so as to afford less resistance to distension during the passage of the foetal head.

Considerable discussion has taken place as to the cause for the onset of the processes, comprised under the heading of labour or parturition, and which occur at a nearly constant period of two hundred and seventy-two days after conception. Most of the explanations which have been suggested, such as the

great irritability of the uterus at the termination of pregnancy, the loosening of the foetal membranes, the return of the menstrual congestion after ten months, thrombosis of the placental sinuses, simply replace one question by another. According to Spiegelberg, the phenomena accompanying the birth of twins, which are often born at a considerable interval from each other, the onset of contractions of the uterus at the right time in extra-uterine, as well as in normal foetation, the fact that the extra-uterine foetus dies when it has become mature, all go to show that the reason why labour occurs at a definite time must be sought for in extrinsic or foetal rather than in uterine, changes. This author suggests that some substances, which had previously been used up by the foetus, gradually accumulate in the maternal blood as the foetus becomes mature, and provoke, by their direct action on the uterus or spinal cord, the uterine contractions which give rise to labour.

It may be that ovarian changes are responsible. It is certain that œstrin injections bring about parturition at any stage of pregnancy, and it is not impossible that a sudden augmentation in the activity of the anterior pituitary, by inducing accelerated production of œstrin by the ovary, may overcome the inhibitory action of the corpus luteum and precipitate parturition. Alternatively, according to Dixon and Marshall, an extract of ovaries given just before parturition has an excitant effect upon the posterior pituitary gland, causing a discharge of its active principle into the cere-

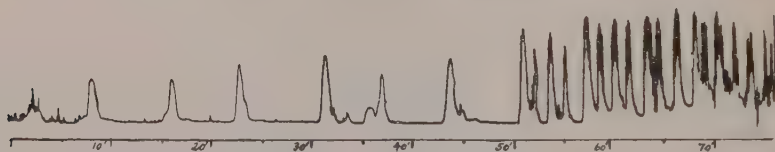


FIG. 542. Record of intra-uterine pressure of woman in labour. (BOURNE and BURN.) Note first stage pains up to the 50' mark. Second stage pains recorded during next twenty-five minutes; they begin suddenly. The head of the child was born at 75' where the pressure momentarily drops, and the body just after the last rise of the lever. The patient was a multipara.

brospinal fluid, whence the pituitrin passes into the blood and excites active uterine contractions. It is unquestionable that the administration of pituitary extract (oxytocic fraction) causes rhythmic contractions of the parturient uterus very similar to those of normal labour (Burn and Bourne). Burn finds that, in presence of œstrin, the effect of pituitary extract on the isolated uterus is greatly enhanced.

Actual parturition, in the woman, is generally divided into three stages. In the first stage the contractions are confined to the uterus, and chiefly act in dilating the os uteri. In this dilatation two factors are involved, namely, the active dilatation brought about by the contraction of the longitudinal muscular fibres which form the chief constituent of the lower part of the uterine wall; and in the second place, a passive dilatation by the pressure of the foetal bag of membranes, which is filled with amniotic fluid, and forced down as a fluid wedge into the os by the contractions of the uterine fundus. The uterine contractions are essentially rhythmical, being feeble at first, and increasing gradually in intensity to a maximum which endures a certain time, and then gradually subsides. The frequency and duration of the contractions increase as labour advances.

The second stage begins as soon as the os uteri is fully dilated and the foetal head has entered the pelvis, when the contractions change in character, being much more prolonged and frequent ('labour pains') and attended by more or less voluntary contractions of the abdominal muscles. This action of

the abdominal muscles is associated with fixation of the diaphragm and closure of the glottis, so that pressure is brought to bear on the whole contents of the abdomen, including the uterus. No expelling force can be ascribed to the vagina, since it is too greatly stretched by the advancing foetus. In this way, the foetus is gradually thrust through the pelvic canal, dilating the soft parts which impede its progress, and is finally expelled through the vulva, the head normally being born first (Fig. 542). The membranes generally rupture towards the end of the first stage of parturition.

A third stage of labour is generally described. This consists in a renewal of uterine contractions about twenty to thirty minutes after the birth of the child, and results in the expulsion of the placenta and decidual membranes.

NERVOUS MECHANISM. We possess little experimental knowledge of the nervous mechanism of parturition. The most important observation on this point is an experiment by Goltz, in which this physiologist observed the normal occurrence of heat, impregnation, and parturition in a bitch whose spinal cord had been completely divided in the dorsal region during the previous year. On the other hand, destruction of the lumbo-sacral cord completely abolishes the normal uterine contractions of parturition, so that this act must be regarded as essentially reflex, presided over by a controlling 'centre' in the grey matter of the cord. The activity of the centre can be inhibited or augmented by impulses arriving at it from the peripheral parts of the body, as by the stimulation of sensory nerves, or from the brain, as under the influence of emotions. The nerve paths from the centre to the uterus have been already described.

CHAPTER XLV

THE SECRETION AND PROPERTIES OF MILK LACTATION

DURING pregnancy, the foetus obtains the whole of its nourishment from the mother by means of the placenta. After birth the quality of the nutriment supplied to the young child depends on the activity of the cells of the mammary glands. Nutrition now involves further activity on the part of the infant, the alimentary canal being concerned in the digestion of the milk supplied by the mother, and the excretory organs, especially the kidneys, being made use of for getting rid of waste material.

The preparation of the mammary glands for the subsequent nourishment of the newborn child begins in the first month of pregnancy, and is marked by swelling of the glands, rapid proliferation of the duct epithelium, and production of many new secreting alveoli. The development of these glands in the rabbit has been already described, and there is no doubt that, in the human species, the process follows very much the same course, being, however, spread over nine months instead of four weeks, as is the case with the rabbit. During the latter half of pregnancy, a watery fluid can generally be expressed from the nipple. In certain mammals, this watery secretion gives place to a secretion of true milk at the end of gestation or during the process of parturition itself. In the woman, though the formation of milk may be hastened if a child has been put to the breasts during the latter part of pregnancy, secretion normally begins on the second or third day, even if the child has been born dead and no attempt at suckling has taken place. For the maintenance of the secretion, the process of suckling is absolutely necessary. If the woman does not nurse her child, the swelling of the breasts gradually passes off, the milk disappears, and the glands undergo a process of involution. Under normal conditions the secretion of milk lasts for six to nine months, and may in rare cases extend over more than a year. The amount secreted increases at first with the growth and size of the child. The Table below represents the average amount of milk secreted

TABLE SHOWING AMOUNT OF MILK SECRETED BY A NURSING WOMAN

INCREASE							Milk secreted daily
Time							20 grammes.
1st day	.	.	.	.	.	.	97
2nd "	.	.	.	.	.	.	211
3rd "	.	.	.	.	.	.	326
4th "	.	.	.	.	.	.	364
5th "	.	.	.	.	.	.	402
6th "	.	.	.	.	.	.	478
7th "	.	.	.	.	.	.	502
2nd week	.	.	.	.	.	.	572
3rd-4th week	.	.	.	.	.	.	736
5th-8th "	.	.	.	.	.	.	797
9th-12th "	.	.	.	.	.	.	836
13th-16th "	.	.	.	.	.	.	867
17th-20th "	.	.	.	.	.	.	944
21st-24th "	.	.	.	.	.	.	963
25th-28th "	.	.	.	.	.	.	

DECREASE					
Time					Milk secreted daily
29th-32nd week	.	.	.	.	916 grammes.
33rd-36th "	.	.	.	.	909 "
37th week "	.	.	.	.	885 "

during the thirty-seven weeks after birth. It will of course be greater with strong, big children, and smaller with weakly children.

COLOSTRUM. Before the secretion of true milk begins, the fluid which is obtained from the breasts is known as colostrum. It may be expressed from the breasts immediately after birth and is ingested by the child during the first two days after birth. The colostrum is formed only in slight quantities. It is an opalescent fluid, often somewhat yellowish, containing fat globules which, if the fluid be allowed to stand, form a yellowish layer on the top. Under the microscope, in addition to the fat globules, may be seen the so-called colostrum corpuscles, which are multinucleated cells loaded with particles of fat. They are probably leucocytes or phagocytes which have wandered into the alveoli and have taken up fat globules. Some of the corpuscles may be desquamated secretory cells. Colostrum is distinguished from true milk by containing little or no caseinogen. It contains about 3 per cent. of proteins, namely, lactalbumin and lactoglobulin, which coagulate on boiling. Lactose and salts are present in the same proportions as in ordinary milk. It is popularly supposed to have a laxative effect on the child.

PROPERTIES OF MILK

Fully formed milk presents certain features which are common to all mammals. These have been chiefly studied in the case of cow's milk. We may therefore deal with the composition of cow's milk and point out later in what respect human milk differs therefrom. Milk is an opaque, white fluid, with characteristic odour and sweetish taste. Its specific gravity varies between 1028 and 1034. Its reaction to litmus is neutral, to methyl orange it reacts alkaline, and to phenolphthalein acid. The $pH = 6.6-6.8$, and, as it contains buffers, *e.g.* phosphates and caseinogen, it may be titrated with suitable indicators, against either acids or alkalis. One hundred cubic centimetres of fresh milk, when treated with methyl orange, require 41 c.c. $n/10$ acid for neutralisation. When treated with phenolphthalein the same amount requires 18 $n/10$ alkali for neutralisation. When exposed to the air, milk rapidly undergoes changes in consequence of infection by micro-organisms. The most common of these changes is the formation of lactic acid by the *bacillus lacticus*. In some cases the milk may undergo a species of alcoholic fermentation, as in the formation of *kephir*, which is made by the fermentation of mare's milk.

The opaque appearance of milk is due chiefly to the presence of multitudes of fine fatty particles. On allowing the milk to stand, the particles rise to the surface, forming cream, and by mechanical agitation, especially if the milk is slightly sour, they may be caused to run together with the formation of butter. Much discussion has arisen as to the reason why the fat globules do not run together naturally. By many authors it has been imagined that they are clothed with a special protein membrane (*haptogen* membrane) originating from the protoplasm of the cell in which the fat globules were originally formed. It must be remembered that in any protein solution, such as that in which the globules are suspended, the protein tends to aggregate, with the formation of a pellicle, at the surface, so that an emulsion once produced in such a fluid will tend to be more or less permanent. There

seems no reason to assume the presence of a distinct membrane differing in composition from the proteins present in the surrounding fluid. The fats of milk consist for the greater part of the neutral glycerides, tripalmitin, tristearin, and triolein. In smaller quantities it contains the triglycerides of myristic acid, butyric acid, and caproic acid, with traces of caprylic, capric, and lauric acids.

The milk plasma, the fluid in which the fat globules are suspended, contains various proteins, a carbohydrate (lactose), and inorganic salts, with a small amount of lecithin and nitrogenous extractives.

THE PROTEINS OF MILK. The chief protein of milk is *caseinogen*, belonging to the class of phosphoproteins. Like other bodies of this class, it presents distinct acid characteristics, being precipitated by acids and soluble in dilute alkalis. It may be prepared from separated milk by the addition of weak acids. A convenient method is to dilute one litre of milk with ten litres of distilled water and add to the mixture 10 c.c. of glacial acetic acid. The precipitate which is formed rapidly sinks to the bottom and may be washed two or three times by decantation. It may be purified by solution in dilute ammonia and precipitation by acetic acid two or three times. The precipitate finally obtained is extracted with alcohol and ether, and the dried caseinogen prepared in this way forms a snow-white powder which is practically insoluble in water and dilute salt solutions. It is easily dissolved on the addition of a little alkali, when it yields solutions which are acid to litmus. When rubbed up with chalk it dissolves, displacing the carbonic acid and forming a calcium caseinogenate. A solution of caseinogen in soda or potash is transparent and passes easily through a clay cell. The calcium caseinogenate forms only opalescent solutions. Apparently the compound is dissociated by water with the formation of caseinogen acid which is in a state of partial solution as swollen-up aggregates. It is impossible, therefore, to filter calcium caseinogenate through a clay cell. It is mainly in this form that caseinogen is contained in milk, hence the opalescent appearance of the milk plasma. When calcium caseinogenate solution is boiled, it forms a pellicle on the surface in the same way as milk does. On treating the caseinogen with rennet, it is converted into a modification known as *paracasein*, which in the presence of calcium salts is thrown out as insoluble casein. To this process is due the clotting of whole milk by rennet, which is made use of in the preparation of cheese, the curd consisting of a network of casein enclosing fat globules in its meshes. On allowing the clot to stand it shrinks, pressing out a milk serum.

From the milk serum or whey may be obtained two other proteins, known as *lactalbumin* and *lactoglobulin*. These resemble very nearly the albumin and globulin of blood serum. They are coagulated on heating. According to some authors a third protein is present in the whey, to which the name whey protein has been given, and which is supposed to be split off from the caseinogen under the action of rennin.

Milk can be boiled without undergoing any coagulation. If it be allowed to stand and become sour by the formation of lactic acid, at a certain degree of acidity boiling the milk causes its complete coagulation. Later on the acid produced is sufficient in itself to precipitate the caseinogen. Both these processes—namely, coagulation of half-sour milk by heating, and spontaneous clotting of milk by the production of acid—are made use of in different countries for the manufacture of cheese.

MILK SUGAR. The sugar of milk, or lactose, is most easily obtained from whey, which, after separation of the clot, is boiled to precipitate the

remaining proteins. On filtering and evaporating slowly, the milk sugar crystallises out. Lactose is a disaccharide and has the formula $C_{12}H_{22}O_{11}$. It is only known to occur in milk. It may be found in the urine of nursing women when the breasts are not kept empty, so that there is reabsorption of the lactose formed in the mammary glands. It is unaltered by ordinary yeast, so that the yeast test is the best means of distinguishing lactose from glucose in the urine. It gives the ordinary tests for reducing sugar. The salts of milk include calcium, sodium and potassium salts, phosphates and chlorides.

Mere enumeration of the constituents of milk presents but little interest unless we realise how closely the composition of this fluid is adapted to the needs of the growing animal. In the first place, we find a proportionality between the totalsolids of the milk and the rate at which the young animal grows. It must be remembered that the milk taken by the animal serves only in part for the production of energy in its body, a great proportion of it being required for the building up of new tissue. In no respect is this correspondence seen better than in the comparative analyses of the ash of milk and of the young animal of the same species which were made by Bunge. The following Table shows the composition of the ash of a rabbit fourteen days old, of the milk which it was receiving from its mother, of the ash of rabbit's blood and blood serum. Nothing could be more striking than the marvellous way in which the cells of the mammary gland have picked out, from the salts of the circulating plasma, exactly those salts which are needed for the growing animal, and in the same proportion :

	Rabbit 14 days old	Rabbit's milk	Rabbit's blood	Rabbit's blood serum
Potash	10.8	10.1	23.8	3.2
Soda	6.0	7.9	31.4	54.7
Lime	35.0	35.7	0.8	1.4
Magnesia	2.2	2.2	0.6	0.6
Iron oxide	0.23	0.08	6.9	0
Phosphoric acid	41.9	39.9	11.1	3.0
Chlorine	4.9	5.4	32.7	47.8

This close correspondence is necessary only where growth is very rapid, so that the greater part of the constituents of the milk have to be utilised in the building up of the animal tissues. As Bunge has shown, the slower the growth of the animal the greater the divergence between the composition

	Rabbit 14 days old.	Rabbit's milk	Puppy few hours old	Bitch's milk	Infant some minutes after birth	Human milk	Cow's milk
Potash	10.8	10.1	11.4	15.0	8.9	35.2	22.1
Soda	6.0	7.9	10.6	8.8	10.0	10.4	13.9
Lime	35.0	35.7	29.5	27.2	33.5	14.8	20.0
Magnesia	2.2	2.2	1.8	1.5	1.3	2.9	2.6
Iron oxide	0.23	0.08	0.72	0.12	1.0	0.18	0.04
Phosphoric acid	41.9	39.9	39.4	34.2	37.7	21.3	24.8
Chlorine	4.9	5.4	8.4	16.9	8.8	19.7	21.3

of the milk and that of the new-born animal. We may compare for instance the rabbit, which doubles its weight in six days, with the dog, which doubles

its weight in ninety-six days, and the human infant, which takes one hundred and eighty days to double its weight at birth.

The last column of the Table on p. 1011 represents the composition of the ash of cow's milk, and shows how very inefficiently this milk can be regarded as replacing human milk, the natural food of the infant.

The relation between rate of growth and protein content of food is well illustrated by a comparison of the composition of the milk in different animals. In the following Table (Proscher) it will be seen that the more rapidly an animal grows the greater is the protein content of the milk with which it is supplied :

	Time in which the body weight of the newborn animal was doubled. Days.	100 parts of Milk contain			
		Protein	Ash	Lime	Phosphoric acid
Man	180	1.6	0.2	0.328	0.473
Horse	60	2.0	0.4	1.240	1.310
Cow	47	3.5	0.7	1.600	1.970
Goat	19	4.3	0.8	2.100	3.220
Pig	18	5.9	—	—	—
Sheep	10	6.5	0.9	2.720	4.120
Dog	8	7.1	1.3	4.530	4.930
Cat	7	9.5	—	—	—

We should expect that the milk, which is the sole food of the growing infant, would contain a relatively greater proportion of protein than is necessary in the case of the adult. In an experiment by E. Feer, quoted by Bunge, a child weighing 8226 grammes at the thirtieth week took 951 grammes of milk. Human milk contains :

Protein	1.6 per cent.
Fat	3.4 "
Sugar	6.1 "
Ash	0.2 "

The child was therefore receiving daily :

Protein	15.2 grammes.
Fat	32.3 "
Sugar	58.0 "
Ash	1.9 "

According to the same proportions a man of 70 kilos. would take in :

Protein	129 grammes.
Fat	275 "
Sugar	494 "
Ash	16 "

It is interesting to note that the protein of this diet differs but little from that in the diets ordinarily accepted as standard, but there is a large excess in the fat and in the total Calorie value, as would be expected from the more rapid metabolism and the relatively larger body surface of the young child.

The fitness of caseinogen for building up the tissues of the body is evident when we compare, as in the following Table, the products of its hydrolysis with those of the proteins in other foodstuffs. It will be seen that practically every amino-acid and allied substance employed in the building up of the various proteins is represented in caseinogen. The only exception is glycine, which can be easily formed from other amino-acids.

CHEMICAL CONSTITUTION OF DIFFERENT PROTEINS

	Serum	Hæmoglobin	Serum-albumin	Serum-globulin	Casinogen	Legumin	Gladin wheat	Avenin oats	Gelatin	Silk-fibroin	Ox muscle
Glycine . . .			0	3.5		0.4	0.1	1.0	16.5	36.0	2.0
Alanine . . .		4.19	2.7	2.2	0.9	2.0	2.0	2.5	0.8	21.0	3.7
Valine . . .	4.3			+	1.0		0.3	1.0	1.0		0.9
Leucine . . .		29.04	20.0	18.7	10.5	8.0	5.6	15.0	2.1	1.5	11.1
Isoleucine . .											
Phenylalanine .		4.24	3.1	3.8	3.2	3.7	2.4	3.2	0.4	1.5	3.1
Tyrosine . . .		1.33	2.1	2.5	4.5	1.5	1.2	1.5		10.5	2.2
Serine . . .	7.8	0.56	0.6		0.2	0.5	0.2		0.4	1.6	
Cystine . . .		0.31	2.5	0.7	0.6		0.5			0	
Proline . . .	11.0	2.34	1.0	2.8	3.1	3.2	7.0	5.4	5.2	+	5.1
Hydroxyproline		1.04			0.2				3.0		
Aspartic acid .		4.43	3.1	2.5	1.2	5.3	0.6	4.0	0.6	+	4.1
Glutamic acid .		1.73	7.7	8.5	11.0	13.8	37.4	18.4	0.9		15.1
Tryptophane .		+	+	+	1.5	+	+			0	+
Arginine . . .	87.4	5.42			4.8	10.1	3.2		7.6	1.0	7.1
Lysine . . .	0	4.28			5.8	4.3	0.0		2.8	+	7.1
Histidine . .	0	10.96			2.5	2.5	1.0		0.4	+	1.1
Ammonia . .					1.6	2.0	5.1		0.4		1.0

In another point we find an adaptation of the milk to the growth of the young animal, and that is in its lecithin content. Lecithin is probably employed to the largest extent in the building up of the central nervous system, where it forms the most important constituent of the medullary sheaths of the nerve fibres. There is a corresponding proportionality between the lecithin content of milk and the relative brain weight of the young animal. Thus in the calf the brain is only $\frac{1}{370}$ of the whole animal. In cow's milk lecithin is present in the proportion of 1.4 per cent. of the total protein. In the puppy the brain is $\frac{1}{30}$ of the whole body and the proportion of lecithin to protein in the milk is 2.11 per cent. In the infant the brain forms $\frac{1}{7}$ of the body weight, while the lecithin is 3.05 per cent. of the protein of human milk.

	Calf	Puppy	Infant
Relative brain weight	1 : 370	1 : 30	1 : 7
Lecithin content of milk in percentage of protein	1.40	2.11	3.05

We thus see that, under normal conditions, the young animal is supplied, through its natural food, with all the foodstuffs in the proportions which it requires for its normal nourishment and growth. It is impossible, therefore, satisfactorily to replace the natural milk of an animal by that of another species. In civilised communities it is becoming more and more the custom to endeavour to feed the child with cow's milk, more or less modified, in the vain endeavour to reproduce the properties of human milk. Among all classes, this involves the administering of a milk differing in its qualities and in the relative proportions of its proteins, fats, carbohydrates, and salts, from human milk. So-called 'humanised' milk is only a rough imitation of the natural mother's milk. Among the poorer classes this artificial feeding means the replacement of a natural sterile food, throwing very little

work on the digestive organs of the child, by a foreign milk, very difficult to digest and often teeming with micro-organisms. There is no doubt that, of the children dying during the first year of life, four-fifths are murdered by this unnatural method of feeding. In some cases it is necessary to adopt artificial feeding because the mother is abnormal, and there is an insufficient secretion of milk. It is therefore important to know what are the main differences in composition between human and cow's milk. In human milk, the caseinogen is, not only absolutely, but also relatively, less than in cow's milk, while the latter is relatively poorer in milk sugar. Human milk is poorer in salts, especially in lime, containing only one-sixth of the amount present in cow's milk. The main differences may be summarised as follows :

	Water	Proteins		Fat	Milk sugar	Salts
		Caseinogen	Albumin			
Human milk. . .	88.5	1.2	0.5	3.3	6.0	0.2
Cow's milk . . .	87.1	3.02	0.53	3.7	4.8	0.7

The caseinogen of human milk presents several points of difference from the caseinogen of cow's milk. It is less easily precipitated by acids. When coagulated by rennet it does not form a firm clot, but is thrown out in a flocculent form. It is thus much more susceptible to the action of gastric juice. Whereas the caseinogen of cow's milk generally gives a precipitate of ' pseudonuclein ' on digestion with pepsin and hydrochloric acid, a smaller or no precipitate is formed with human caseinogen.

Another important advantage of human milk for the infant lies in the presence of antitoxins. It has been shown by Ehrlich that, when a female animal has been immunised against any toxin and has in consequence produced antitoxins in its blood, these antitoxins will, if it has young, pass over into the milk. The same passage of anti-bodies into the milk has been proved in the case of various infective disorders. The ingestion of human milk will, therefore, not only nourish the infant, but will provide it with a certain measure of passive immunity against possible infection by diseases to which its species is liable.

THE SECRETION OF MILK. When fully formed, each mammary gland consists of fifteen to twenty lobes embedded in connective tissue. Each lobe is made up of a mass of secreting alveoli, which lead by narrow ducts into one large lactiferous duct. These lactiferous ducts, one from each lobe, open on the nipple, undergoing in the nipple itself an oval enlargement. Before secretion begins, the alveoli as well as the ducts are lined with a cubical epithelium. When secretion commences, a marked difference develops between the epithelium of the alveoli and that of the ducts. While that of the latter retains its previous character, the cells of the secreting epithelium grow in length and project into the lumen of the gland. In the innermost part of the protoplasm numerous fat globules make their appearance. If sections of the gland be made during the various stages of its activity, and stained by Altmann's method (acid fuchsin and picric acid), it will be seen that the commencement of activity is marked by the growth of the innermost part of the cells and the development in these of a number of granules (Fig. 543). These granules finally lengthen into shapes like spirilla, while others of them form fat and become metamorphosed into fat granules. The nuclei

of the cells also divide, apparently in preparation for the replacement of some cells which undergo complete degeneration and are cast off into the secretion.

We know very little about the mechanism of milk secretion. It seems impossible at present to explain the very close adaptation between the activity of the secretory cells and the needs of the infant or young animal. Two at least of the constituents of milk, caseinogen and lactose, are peculiar to this secretion. It would seem that the caseinogen is produced by the gland cells by synthesis from the amino acids of the blood stream, and that the lactose is derived, also by synthesis, from the blood sugar. The fat similarly originates in the blood fat, and much of it ultimately in the fat of the food, or of the body depots: how this is transferred to the milk remains a mystery.

The growth of the mammary glands during pregnancy is largely determined by some form of chemical stimulation, the specific hormone being produced in

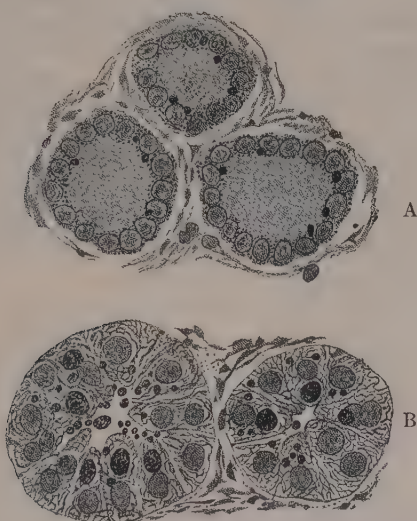


FIG. 543. Sections of Mammary Gland of Guinea-pig (fat granules stained black with osmic acid).

A. During rest. B. During active secretion. It will be noticed that in this case the active formation of products of cell metabolism (granules, &c.) begins with the commencement of secretion, and does not occur almost exclusively during rest, as in the salivary glands. In the mammary gland, the active growth of protoplasm, the formation of granules from the protoplasm, and the discharge of these granules in the secretion appear to go on at one and the same time.

the corpus luteum of the ovary. It has been suggested by Hildebrandt that this stimulus is inhibitory in character—inhibitory, that is to say, of secretion—and therefore tending to the continuous growth of the gland cells. With the expulsion of the foetus at birth the source of the inhibitory stimulus is removed and the overgrown gland cells enter into a condition of spontaneous activity. However this may be, there is no doubt that the secretion of the gland, once formed, is continued independently of the foetus, or, indeed, of any of the pelvic organs. Removal of the ovaries in a cow is, in fact, sometimes employed as a means of prolonging the secretion of milk. The only condition in the human being, which is necessary for secretion to continue during six to nine months after birth, is the repeated emptying of the gland, *i.e.* the removal of the secreted milk. The process of suckling not only removes the milk already secreted but excites

the secretion of more milk. The secretion is certainly subject to nervous influences, but physiologists have not succeeded either in producing secretion by stimulation of the nerves going to the glands, or in stopping secretion by section of these nerves. Moreover the food of the animal may be varied within very wide limits without altering the composition or amount of the milk secreted, provided that the food is sufficient in amount. The only constituent of the milk for which we have direct evidence of alteration by changes in the food supply of the mother is the fat. It is well known that the composition of butter may be affected according to the food supplied to the cow. A large supply of oilcake, for instance, may result in the production of a butter which is deficient in the saturated fatty acids and is therefore oily at ordinary temperatures. Abnormal fats and fatty acids such as iodised fats or erucic acid, when administered to an animal in lactation, may appear among the fats of the milk. Not only can the secretion and composition of the milk be affected reflexly through the nervous system, as *e.g.* under the influence of emotions, but the influence may be reciprocal. This is especially marked in the case of the pelvic organs. The act of suckling excites tonic contractions of the uterus. Putting the child to the breast shortly after birth is, therefore, an important means of causing contraction of the uterus, and stopping any tendency to hæmorrhage from the venous sinuses opened by the separation of the placenta and foetal membranes. The nursing of the child is thus an important means of procuring a proper involution of the uterus after labour. Many uterine troubles among women may be ascribed to the previous neglect of this elementary duty.

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